

Clinical Features, Digital Subtraction Angiography Findings, And Risk Factors Of Cerebral Venous Sinus Thrombosis: A Single Centre Study

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Abstract

Introduction: Cerebral Venous Sinus Thrombosis (CVST) is considered one of rare causes of stroke caused by intracranial vein, including cerebral sinuses, cortical vein and proximal part of the jugular vein, but delay in diagnosing and treating can result in brain infarct with hemorrhagic transformation, even death. Digital Subtraction Angiography (DSA) is an invasive diagnostic technique used to clearly delineate cerebral veins.

Objective : To learn the clinical characteristics of patients with CVST that had been confirmed by Digital Subtraction Angiography (DSA).

Method: Retrospective observational descriptive study from hospitalized CVST patients in Neurology ward Hasan Sadikin General Hospital from June 2015 to July 2020 were obtained and analyzed.

Results: There were 61 subjects with most (66.7%) being women between 40-49 years old with most frequently found risk factor was infection (24.2%) and prothrombotic conditions (18.2%). Thrombosis sinus involved were the transverse sinus (88%), cavernous sinus (9%), and sagittalis sinus (1%) with commonly reported symptoms were headache (81.85%) and motoric weakness (18.2%). D-dimer levels were also increased with mean 1.21 mg/dl.

Conclusion: CVST patients are mostly in women at the middle age of fifth decade, and infection being the most frequent risk factors. Headache and hemiparesis were the most frequent clinical manifestation. Location of thrombosis were more often found on the transverse sinus and D-Dimer level was increased from laboratory examination in the study subject.

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a disease resulting from occlusion of intracranial vein structures, including the cerebral sinuses, cortical veins, and the proximal jugular vein. CVST is a rare case with an incidence of less than 1%. CVST is more often found in patients less than 50 years old, especially women, patients with thrombophilia and pregnant women or who use hormonal contraceptives. Neuroimaging investigation techniques are needed to help establish the diagnosis of CVST and delay in diagnosis and therapy can lead to complications such as bloody infarction and even death.¹

A retrospective study of hospitals in Saudi Arabia from 1985 to 1994 estimated the incidence of less than 10 cases per

million people per year old, a prospective study of 122 patients between 2001 and 2004 in Isfahan, Iran, reporting 12.3 cases per million people. per years old, a retrospective multicenter study in the Netherlands of 94 patients over the years 2008 to 2010 reported 13.2 cases per million people per years old, and a new prospective study from Hamadan, Iran, of 151 cases between 2009 and 2015 reported 13.5 cases per million per years old.¹ A study in Australia (Adelaide) of 7 public hospitals from 2005 to 2011, namely 105 adult cases, representing 15.7 cases per million population per year old with almost the same sex distribution (52% women). With this research reflects a better diagnostic and management strategy.¹⁻⁴

The clinical signs and symptoms of CVST vary widely, they can be acute, subacute or chronic. Clinical signs and

symptoms are mainly headache, may be accompanied by seizures, but may also not be specific so that making a diagnosis based on radiological images as early as possible is very important and specific management can be given as soon as possible. due to certain diseases or conditions as mentioned in the risk factors for CVST. A prothrombotic condition is an abnormal condition in which there is an increase in blood coagulation factors which increase the risk of thrombosis.¹⁻⁴

Digital Subtraction Angiography (DSA) is an invasive diagnostic technique used to clearly delineate veins. Even so, the DSA is still considered a gold standard inspection. When there is a clinical suspicion in a CVST patient, but from the results of magnetic resonance venography (MRV) or computed tomography venography (CTV) no abnormalities are found, then DSA is the choice.^{3,7} Research on CVST has never been done in Indonesia, so researchers are interested in know how the clinical characteristics of CVST have been confirmed by the DSA examination to help make the diagnosis, so that management can be given quickly and prevent the incidence of complications and recurrences. This study is expected to provide an overview of the characteristics of clinical signs and symptoms of CVST patients.

METHODS

This was a retrospective, observational descriptive study of the medical records of patients who have been diagnosed with CVST in the Neurology ward of Hasan Sadikin Hospital Bandung, Indonesia. Data were collected from the patient's medical records by total sampling with a final diagnosis of CVST based on the results of the DSA examination who were treated or came to the neurological clinic at Hasan Sadikin Hospital, Bandung. The collected data were grouped, edited and processed using the SPSS version 25 windows program. This study had been approved by Hasan Sadikin Ethical Research Committee (LB.02.01/X.6.5/315/2020). This study had complied with all relevant ethical regulation (including The Declaration of Helsinki). All patients were informed about the purpose of the study and had obtained written consent.

RESULTS

Medical records that meet the inclusion and exclusion criteria starting from June 2015 to July 2020, obtained of 61 patients, most of the CVST patients occurred in the age range of 40-49 years old as many as 15 people (24.2%).

Characteristics based on gender shows that more women experience CVST (72.3%) compared to men (27.8%). Characteristics based on risk factors were obtained from the patient's medical record and re-history, the risk factors for infection were more than 15 people (24.2%) consisting of ear, sinus cavity and mastoid infection, followed by prothrombotic conditions 11 people (18.2%) consisted of deficiency protein C and S and others with increased D-dimer levels, the cause is not known, hormone therapy 4 people (6.1%) due to the use of oral contraceptives, systemic disease 4 people (6.1%) consisting of patients suffering from Systemic Lupus Erythematosus (SLE), malignancy 4 people (6.1%) consisted of patients with a history of breast tumors and lymphoma then 2 people (3.0%), namely patients suffering from Autoimmune Hemolytic Anemia (AIHA) caused by SLE who were being suffered by CVST patients (table 1).

Characteristics based on clinical signs and symptoms can be seen that the clinical symptoms of headache symptoms most often found by CVST sufferers were 36 people (81.8%), followed by hemiparesis (33.3%), vertigo (27.3%), tinnitus (6.1%), diplopia (3.0%), visual impairment (3.0%) and seizure (3.0%) (see table 3).

Clinical Characteristics of CVST Patients Based on DSA Features

In this study, most of thrombosis in transverse sinus (88.0%), followed by cavernous sinuses and sagittal superior sinus. (see table 2).

Characteristics of symptoms and clinical signs based on DSA features in CVST patients with thrombosis in the transverse sinus can be seen complaints of headache are often found, followed by hemiparesis, vertigo and cranial nerve palsy. Whereas in the thrombosis in the cavernous sinus, headache complaints were also common, followed by vertigo, hemiparesis and cranial nerve palsy (see table 3).

Characteristics of Laboratory Examination Results of CVST Patients

In the laboratory results performed before the diagnosis of CVST, it can be seen that the prominent result is an increase in the patient's D-Dimer level with an average of 1.21 mg / L, as in table 4.

Table 1

Clinical characteristic of research subjects

| Clinical characteristic | n=61 | (%) |
|----------------------------|------|------|
| Age | | |
| < 20 years old | 4 | 6 |
| 20 – 29 years old | 11 | 18.1 |
| 30 – 39 years old | 11 | 18.1 |
| 40 – 49 years old | 15 | 24.2 |
| 50 – 59 years old | 12 | 21.2 |
| > 60 years old | 8 | 12.1 |
| Gender | | |
| Male | 17 | 33 |
| Female | 44 | 66.7 |
| Risk factors (n=40) | | |
| Infection | 15 | 24.2 |
| Prothrombotic state | 11 | 18.2 |
| Hormonal treatment | 4 | 6.1 |
| Malignancy | 4 | 6.1 |
| Autoimmune disorders | 4 | 6.1 |
| Hematology disorders | 2 | 3 |

Table 2

DSA findings of research subjects

| Thrombosis location | n = 61 | % |
|--------------------------|--------|------|
| Transversus sinus | 54 | 88.0 |
| Cavernosus sinus | 6 | 9.0 |
| Sagitalis superior sinus | 1 | 1.0 |

Table 3

Clinical features regarding DSA findings

| Sign and symptoms | Location of thrombosis sinus | | |
|---------------------|-------------------------------|-----------------------------|--------------------------------------|
| | Transversus sinus (n = 54) | Cavernosus sinus (n = 6) | Sagitalis superior sinus (n=1) |
| Headache | 31 (82.1%) | 4 (80%) | 1 (100%) |
| Hemiparesis | 9 (31.1%) | 2 (40%) | |
| Vertigo | 6 (21.4%) | 3 (60%) | |
| Cranial nerve palsy | 5 (17.8%) | 2 (40%) | |
| Tinnitus | 2 (7.1%) | - | |
| Diplopia | 1 (3.5%) | - | |
| Visual impairment | 1 (3.5%) | - | |
| Seizure | 1 (3.5%) | - | |

Table 4

Laboratory findings of Research Subjects

| Laboratory | Mean | Range | Normal value |
|-------------|--------------------------|------------------------------------|---------------------------------|
| Hemoglobin | 13.00 g/dL | 8.6 – 17.6 g/dL | 13.5-17.5 g/dL |
| Hematokrit | 39.47% | 26.6 – 51.00% | 40-52% |
| Leucocyte | 7.700 /mm ³ | 4.800 – 10.300 /mm ³ | 4500-11.000/mm ³ |
| Thrombocyte | 308.000 /mm ³ | 225.000 – 527.000 /mm ³ | 150.000-450.000/mm ³ |
| BSR | 14 mm/lrs | 4 – 23 mm/lrs | 0 – 20 mm/lrs |
| PT | 14.31 seconds | 9.6 – 36.2 seconds | 8.3 – 12.3 seconds |
| APTT | 32.52 seconds | 21.00 – 71.6 seconds | 16.4 – 36.4 seconds |
| INR | 1.14 | 0.53 – 3.63 | 0.83 – 1.17 |
| Fibrinogen | 332.35 mg/dL | 199.2 – 541 mg/dL | 200 – 400 mgdL |
| D-Dimer | 1.21 mg/L | 0.2 – 4.29 mg/L | < 0.55 mg/dL |

Note : BSR: Blood Sedimentaion Rate;PT: Prothrombin Time;aPTT: activated Partial Thromboplastin Time;INR:International Normalized Ratio

DISCUSSION

The age of CVST sufferers occurs in the age range 40-49 years old (24.2%). These results are in accordance with those quoted by Bushnell in 2014 years old who said that CVST occurs more frequently at the age of less than fifty years old.⁸ Based on gender characteristics, the incidence rate of CVST in women is greater than that of men (66.7%). This is in accordance with previous studies which stated that 3 out of 4 people with CVST are women, because of conditions related to pregnancy, the puerperium and use of oral contraceptives.¹

In this study, it was found that patients with risk factors for hormonal disorders caused by the use of oral contraceptives. Research conducted by Rosendaal et al said that women who use oral contraceptives will increase the risk of CVST. The use of oral contraceptives will increase the procoagulant factors VII, X, XII, XIII and reduce the anticoagulant factors, protein S and antithrombin which cause prothrombotic conditions in patients.⁴

When viewed from the characteristics based on risk factors, it can be seen that infection in the sinus cavity and mastoid area is more common, followed by risk factors for prothrombotic conditions. This is due to the lack of awareness and ignorance of the public about infection prevention and the importance of treating infectious diseases which are risk factors for CVST. Research conducted by Bisioendial et al said that from 7 volunteers with high levels of C-Reactive Protein (CRP) caused a significant increase in von Willebrand factor, prothrombin 1 and 2 fragments, D-Dimer and type 1 plasminogen activator inhibitors. CRP will inhibit the expression of plasminogen activator in endothelial tissue which will stimulate platelet adhesion and thrombus growth.⁵⁻⁸

Risk factors for malignancy were also found in this study. In a study conducted by Graham et al, stated that the formation of reactants in the acute phase, abnormal protein

metabolism, necrosis and hemodynamic changes can contribute to activation of coagulation in patients with malignancy. There are two interactions between malignant cells and the hemostasis system, the first is the ability to produce and produce procoagulants and inflammatory cytokines, the second is a direct interaction with other blood cells. The procoagulant activity on tumor cells leads to the formation of fibrin deposits and will activate factor X independently. Inflammatory cytokines will affect the vascular coagulation system, for example tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) which can induce tissue factor (TF) and reduce protein C activation as an anticoagulant. This tissue factor is produced as an inflammatory response which forms a complex with factor VII and initiates the coagulation process by activating factors IX and X.⁹⁻¹²

Risk factors due to systemic disease lupus erythematosus syndrome were also found in this study, these data were obtained from medical records. Li Wang et al from their study said several mechanisms that contribute to CVST, the first is due to damage to endothelial cells caused by immune complex induced vasculitis which is thought to play an important role in the occurrence of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) including CVST. The second mechanism is due to the presence of antiphospholipid antibodies (APL) which is another cause of CVST in SLE. The interaction between endothelial cells and APL will inhibit the function of protein C and protein S which will lead to the formation of thrombus.^{13,14}

Characteristics based on symptoms and clinical signs showed that headache complaints were more than other complaints, namely as much as 81.8%. Transverse sinus thrombus will cause symptoms intracranial hypertension and most often cause headaches. Approximately 90% of patients with cerebral venous thrombus complain of generalized or localized headaches.^{3,15} Then hemiparesis as much as 33.3%, thrombus in the superior and inferior sagittal sinuses can cause motor abnormalities and seizures, because the location of the lesion is close to the area of motor and central cortical-subcortical region.³ Thrombosis in the transverse sinus will interfere with blood flow from the superior sagittal and inferior sagittal sinuses, because the transverse sinus is a continuation of the superior sagittal sinus and the inferior sagittal sinus. So that thrombosis in the transverse sinus can cause the same symptoms.³

Symptoms of visual disturbances are caused by thrombus in

the transverse sinus which will interfere with the absorption of brain fluid by the arachnoid villi, because there are many arachnoid villi in the transverse sinuses so thrombosis at that location will result in hydrocephalus which will compress visual nerve. Complaints of vertigo in the transverse sinuses and cavernous sinuses are caused by the location of the two sinuses close to the VIII nerves, so that if thrombosis occurs it will interfere with back blood flow from the VIII nerves which will cause a balance system disorder, while the symptoms of tinnitus and other cranial nerve palsy are caused by thrombus in the internal jugular vein.³ The internal jugular vein is a continuation of the two branches of the transverse sinus, so thrombus in the transverse sinus will cause tinnitus and cranial nerve palsy. The symptom of diplopia is a sign of paralysis of the eye-moving nerves caused by a thrombus in the cavernous sinus area, because the location of this sinus is in the area behind the eye and is traversed by cranial nerves III, IV and VI.³ Thrombosis in the transverse sinus also causes diplopia symptoms because the cavernous sinus is connected with the transverse sinus, thereby interfering with back blood flow from the cavernous sinuses.¹²

Based on the description of the DSA finding, it can be seen that thrombosis in the transverse sinuses was more prevalent in CVST patients (88%), followed by the cavernous sinus (9%) and sagittal sinus (1%). This is in accordance with a recent study by Wang Li (China), Jerzy (Poland) and research by Ferro et al cited in the article Canhao et al, which found that more thrombosis occurred in the transverse sinuses by 82% and 86%, followed by the sagittal sinus 52.9% and superior sagittal sinus 35.4%. It is also said that infection always causes thrombosis in the transverse sinuses, cavernous sinuses and sagittal sinuses. In some patients, there are anatomical variations such as atresia and hypoplasia of the left transverse sinus. Approximately 10% of cases of CVST are associated with damage to blood vessel walls due to local inflammation (sinusitis and mastoiditis).^{16,17} Sinusitis and mastoiditis will cause vasculitis in the transverse sinus, thereby increasing the risk of thrombosis.

When we viewed from the laboratory abnormalities that stand out from CVST patients is an increase in D-Dimer levels with an average of 1.21 mg / dL. This is in accordance with previous studies which stated that more CVST patients had D-Dimer levels of more than 0.5 mg / dL.^{18,19}

A prospective study conducted on 35 patients found an

increase in D-Dimer levels in 34 patients. Likewise, another study showed an increase in D-Dimer (27 of 30 patients). The results of this study showed a sensitivity rate of 97.2%, a specificity of 91.2% for the D-Dimer examination in CVST patients and had a good predictive value for excluding CVST (negative predictive value was 99.6% and positive predictive value was only 55.7%).⁸ D-Dimer examination is an initial reference for laboratory examinations before moving to the next hematology examination in accordance with the patient's risk factors.

Research Limitations

This study of the clinical signs and symptoms of CVST patients were retrospective so that complete data cannot be obtained. This study did not assess the effect of prothrombotic risk factors on the incidence of CVST and did not assess the relationship between clinical symptoms and clinical features.

CONCLUSION

CVST patients occur in women in the mid-fifth decade and the most risk factor was infection. Headache and hemiparesis are the most frequent symptoms. The location of thrombosis mostly occurs in the transverse sinuses and found an increase in D-Dimer from the results of laboratory tests.

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