Smoker's Cerebral Venous Thrombosis-A Retrospective Study

Sunil Jee Bhat[1], Priyanka V Kashyap[2]

ABSTRACT

Introduction: Cerebral venous thrombosis including venous sinus thrombosis and cortical vein thrombosis is a rare but important cause of headache so in this series, we evaluated the patients of headache secondary to CVT in which polycythemia was the denominator.

Material and methods: A retrospective study was conducted in Shri Mahant Indiresh hospital from January 2012 to January 2014 of 2 years duration in Neurology department in Dehradun. The primary patient pool consisted of 100 patients suffering from headache, enrolled from Out-patient department and In-patient department.

Results: Out of 100 patients, 30 were found to have cortical venous thrombosis (CVT) on MRI brain and venogram. The superior sagittal sinus (SSS) was the most common involved (78%) followed by Transverse and Sigmoid sinuses-22%. In this study, we found that the patients who had headache and CVT had one thing common and that was secondary polycythemia probably secondary to smoking and high altitude region.

Conclusion: Cigarette smoking has been associated with many medical problems, and one of these is polycythemia. This case series demonstrates a common but rarely correlated presentation of smoker's polycythemia.

Keywords: Cerebral venous thrombosis, polycythemia, smoking, headache

INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is a rare initial presentation of polycythemia, originally recognized for more than 150 years presenting as acute or slowly progressive neurological deficit and is lethal if remains undiagnosed.[1] CVST has wide spectrum of signs and symptoms, which evolve suddenly or over the weeks. It is clinically challenging and mimics certain important neurologic conditions such as stroke, encephalitis, meningitis, Benign intracranial hypertension. It has unpredictable outcome and affect all range of age group. CVT is a life threatening condition incidence being 3-4 /million adults.[2] Cerebral venous thrombosis including venous sinus thrombosis and cortical vein thrombosis is a rare but important cause of headache. Though can cause devastating injury to brain, most people have good prognosis if treated early. There are various risk factors causing CVT, these include acquired and congenital diseases, some of them are hypercoagulable disorders such as Factor v Leiden mutation, presence of anticardiolipin antibodies, Antithrombin III gene mutation and polycythemia.[3] A polycythemia related prothrombotic state can also present with CVT.[4] Polycythemia is a rare condition involving myeloproliferative clone cells. Thrombosis is a serious complication of polycythemia and can lead to death in up to 8.3 % patients.[4]

The pathogenesis of thrombotic complications in polycythemia has not yet been clear. The most appropriate mechanism postulated is that leukocytosis increases viscosity thus decreasing blood flow leading to thrombotic events.[5-7] Smoking is also a cause of secondary polycythemia which results due to increased red cell mass and reduced plasma volume due to hypoxia.[3,8] Smoker polycythemia can cause serious initial presentation in form of CVT, but there is limited data. Certain studies have shown correlation of high altitude to polycythemia.[9-11] In this series, we evaluated the patients of headache secondary to CVT in which polycythemia was the denominator.

MATERIAL AND METHODS

We conducted a retrospective study in Shri Mahant Indiresh hospital from Jan 2012 to Jan 2014 of 2 years duration in Neurology department in Dehradun. The study protocol was approved by the Institutional Ethics Committee.

A total of 100 patients were analysed retrospectively from two year records of Out-patient department and In-patient department suffering from headache. Headache character varied from moderate to severe grade and we applied ICD beta 3 classification.[12] Sixty six patients fulfilled criteria of migraine and 34 patients fulfilled the criteria of Tension Type headache. A complete history regarding headache-its onset, character, duration and frequency was taken followed by a detailed physical examination including fundus and signs of meningeal irritation. Papilledema was assessed clinically by ophthalmoscopy. All patients with suspected papilloedema were examined by an ophthalmologist. These patients underwent relevant blood investigations involving complete blood count (CBC) with hematocrit (PCV) and Estimated sedimentation rate (ESR), Biochemisty parameters including Fasting blood sugar FBS, Lipid profile, Thyroid profile, Renal profile. Hypercoagulable profile including protein c, protein s, Factor v Leiden, Antiphospholipid antibody (APLA), platelets, Antithrobin III were conducted. 2 D Echo was performed in all patients.MRI Brain with venogram was performed in all these patients. Routinely T1, T2 weighted images, FLAIR, DWI, and T2* sequences were carried out.

STATISTICAL ANALYSIS

Data analysis was carried out with SPSS software (version 16.0). Statistical analysis of categorical variables was carried out using Fisher's exact test or the Chi-square test. Independent t-test or the Mann-Whitney U test was used for continuous variables. A value of $P \leq 0.05$ was considered significant.

RESULTS

Out of 100 patients, 30 were found to have cortical venous

[1]Senior Resident, [2]Assisstance Professor, Department of Neurology, Shri Mahant Indiresh Hospital, Dehra Dun, India

Corresponding author: A-60, MIG, MDDA Colony, Dalanwala, Dehradun, Uttrakhand; 248001, India

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thrombosis (CVT) on MRI brain and venogram. The superior sagittal sinus (SSS) was the most common involved (78%) followed by Transverse and Sigmoid sinuses-22%. Demographic profile of these patients is shown in Table-1. Echocardiography was normal in all the patients. Of them 26 were smokers, 4 were not smoking. Hemoglobin levels were ranged from 18-26 gm% in these 30 patients having CVT where as it was 13-15 gm% in 70 patients of headache who did not had CVT (Table-2). Hematocrit levels were 56-60 % in CVT patients. It was below 40 in non-CVT group (Table-3). All these patients were resident of high hills in Uttrakhand.

Papilloedema was found in 10 patients of CVT consistent with the diagnosis of Benign intracranial hypertension (BIH). Three out of 10 patients had transverse sinus thrombosis, one had both transverse and sigmoid sinus thrombosis, six had thrombosis of SSS.

In this study, we found that the patients who had headache and CVT had one thing common and that was secondary polycythemia probably secondary to smoking and high altitude region. Four patients who did not had smoking habit and had CVT, we attributed it to hypoxia leading to raised hemoglobin concentration in blood.

DISCUSSION

The venous drainage of the brain is predominantly via the cerebral veins which communicate with the dural sinuses. Deep cerebral veins communicate with the Inferior sagittal and straight sinuses. Superficial cerebral veins (which drain the majority of the cerebral cortex) empty into the superior sagittal sinus which communicates with the transverse sinuses, of which the right is usually dominant. The transverse sinuses communicate with the sigmoid sinuses from which blood drains into the internal jugular veins. Should the superior sagittal sinus be occluded, superior and inferior anastomotic veins provide an alternative route of cortical venous drainage into the cavernous sinuses and transverse sinuses, respectively. With time, further venous collaterals develop and provide a communication between the superficial and deep venous systems.

The majority of CSF absorption is via the arachnoid granulations located mainly within the sagittal and other principal dural sinuses, so changes in cerebral venous pressure affects Cerebrospinal fluid (CSF) pressure. Hence, venous sinus obstruction rapidly leads to cerebral venous hypertension, a rise in cerebral blood volume and elevated CSF pressure. This accounts for the early onset of symptoms and signs suggestive of raised intracranial pressure.[11]

In the present era, the causes of CVT can be grouped broadly into endocrine disturbances, hematological /immunological abnormalities, connective tissue and other inflammatory disorders, and neoplastic causes. Infective etiologies (e.g. meningitis, otitis media, subdural empyema) were over represented in early series and accounted for the apparently high morbidity and mortality (30-50%) of the condition.[13]

The mechanism of sinus occlusion is usually either by the development of a prothrombotic state, by direct disturbance of venous flow (e.g., compression, low flow states), or by infiltration or inflammation of the sinus wall (e.g., the arteritides). Even after full investigation up to 25% of patients with venous sinus occlusion fall into the 'idiopathic' category.[14-16]

Age	Mean age = 34.34
	Median = 33.50
	Mode = 41
	Range = 39
	SD = 9.910
Sex	N (%)
Female	66 (66.0)
Male	34 (34.0)
On MRI	
CVT (SSS, TS,T)	30 (30.0)
Normal	70 (70.0)
PCV	
<50	72 (72.0)
>50	28 (28.0)
Headache	
Migraine	66(66.0)
TTT	34(34.0)
Smokers	
Yes	9 (9.0)
No	91(91.0)
Haemoglobin	
<15	71(71.0)
>15	29(29.0)

Table-1: Demographic profile

Haemoglobin (gm%)	CVT		Total
	Present N (%)	Absent N (%)	
<15	1(1.5)	70 (98.5)	71
>15	29 (100.0)	0(0.0)	29
Total	30	70	
There was significant difference in hemoglobin levels in CVT and Non CVT group (p<.05)			

Table-2: Correlation between Haemoglobin and CVT

PCV	On MRI		Total
	+ve N (%)	-ve N (%)	
<50	2(2.77)	70(97.22)	72
>50	28(100.0)	0(0.0)	28
Total	30	70	100
There was significant difference in Hematocrit values in CVT and non-CVT group.			

Table-3: Correlation between PCV and MRI finding

Smokers	On MRI finding		Total
	+ve N (%)	-ve N (%)	
Yes	8(88.8)	1(11.1)	9
No	22(24.17)	69(75.82)	91
Total	30	70	100
X^2=16.33; df = 1; P<0.001, highly significant, Smokers had more CVT			

Table-4: Correlation between smokers and MRI finding

CVT can be caused by wide range of etiologies including hypercoagulable disorders such as Factor v Leiden mutation, presence of Anticardiolipin antibody, antithrombin III mutation and polycythemia.[17]

The true incidence of cerebral venous occlusion is unknown but it is almost certainly more common then generally appreciated. In our series, 10 out of 30 patients of CVT had presentation of

Benign intracranial hypertension (BIH) and MRI with venogram sequence helped in reaching the cause of it. With the growing use of non-invasive imaging it is apparent that 25% of patients with Benign intracranial hypertension may have underlying CVT. There is a slight female predominance (1.3:1) as also proved in our series probably reflecting oral contraceptive use with its usual onset in the third or fourth decades.[14]

The presentation of CVT may be acute, subacute, or chronic. The most consistent features are headache and papilloedema (at least 75% and 50% of cases, respectively). In patients with a history extending over several weeks, Benign intracranial hypertension-like presentation is more common (headache and papilloedema alone).

In our series, ten patients were having headache of subacute onset with papilloedema consistent with Benign intracranial hypertension and all had thrombosis on MRV.

Venous phase MRA is now of sufficient quality to show characteristic filling defects in the principal dural sinuses. Unlike conventional angiography, MRA is entirely noninvasive and does not require the administration of contrast. In combination with standard T1 and T2 weighted images, it is therefore possible to take angiographic sequences of the venous system as well as making a search for areas of cortical venous infarction which may have been overlooked on CT.

Polycythemia is a myelopoliferative disorder that is caused by a variety of etiology.[18] Primary polycythemia is caused by mutation in the JAK 2 gene.[19] Secondary polycythemia results due to elevated serum erythropoietin levels in response to chronic hypoxia which stimulates excess production of erythrocytes from the bone marrow. Cigarette smoking creates a unique condition of combined polycythemia secondary to chronic hypoxia, leading to raised RBCs, production due to elevated carboxy Hb level with concomittant plasma volume reduction.[17,20]

Smoker's polycythemia can have serious initial presentation in the form of CVT, but data regarding the actual proportion of patients affected is limited. Various published studies suggest that polycythemia can present in a variety of ways but specific initial presentation of smoker's polycythemia with CVT is rare.[21-23]

CVT is a rare but serious complication of polycythemia.[24] Approx 15% of patients of PV group has major thrombotic events in the past. The mechanism by which polycythemia causes thrombosis is still under investigation. Leucocytosis in association with stasis of blood causes hyperviscosity possibly leading to the development of thrombosis.[25-27]

Smoking induced polycythemia is a known condition but its spectrum of presentation is still under reported.

In our study, we aimed to determine the association between smoker's polycythemia and CVT after ruling out common coagulation disorder and primary polycythemia as etiology.

Smoker's polycythemia is usually diagnosed after exclusion of other causes of primary polycythemia such as JAK2 mutation which was not done in our case. It may be possible that the non smoker group may has the same or the smoker polycythemia group may have this overlap is still not ruled out.

Others parameter such as erythropoietin levels, carboxy hemoglobin levels, should also be done concomittant with hemoglobin levels and Hematocrit determination.[20-22]

In our study, smoker's polycythemia was diagnosed based on laboratory findings of raised hemoglobin concentration and hematocrit percentage as compared the non smoker group. Smoker's polycythemia is best diagnosed by a left shifted O_2 dissociation curve which was not done in our series due to some technical constraints. Presence of left shift of the O_2 dissociation curve suggests hypoxia secondary to smoking. International study on cerebral vein and dural sinus thrombosis (ISCVT study) showed mortality upto 8.3% in untreated CVT patients.[28]

Treatment of smoker's polycythemia is usually directed towards the acute treatment of the disease as well as cessation of smoking. In previous studies, smoking cessation resulted in significant decrease in hematocrit and hemoglobin levels.[17,20]The patients presented significant improvement following cessation of smoking and anticoagulation treatment as evident by clinical improvement and radiologic imaging.

In our patients, we treated them with Low molecular weight Heparin (LMWH) in dosage 1mg/kg subcutaneous twice a day was given along with Warfarin overlap of 7 days duration followed by Warfarin alone and INR was maintained at 2-2.5. Anecdotal reports suggest that anticoagulation with intravenous heparin may be of benefit[29,30] and it seems logical to treat thereafter with warfarin according to the underlying etiology. There is preliminary evidence to suggest that heparin improves outcome[31], and it is not necessarily contraindicated in the presence of hemorrhagic venous infarction. By limiting further thrombogenesis within the superficial cortical veins, such patients can have a dramatic response to heparinisation.

Early series of CVT reported mortalities of 30-50% and if left untreated, the condition is potentially life threatening. Recent reports describe mortality rates of 5-30%[32], The better outcome reflects greater awareness amongst specialists (who are more likely to gather larger series),noninvasive imaging techniques (enabling earlier diagnosis and recognition of milder cases), and the relative decline of infective etiologies. Amongst survivors, a minority develop a permanent deficit such as focal limb weakness, epilepsy or optic atrophy. When the question of optimum treatment (antithrombotics, anticoagulants and fibrinolytics) is answered the morbidity and mortality associated with CVT should fall further.

Smoking cessation was done simultaneously and hemoglobin and Hematocrit levels were repeated after a month which showed significant reduction in both the levels.

This series of headache patients revealed that CVT is an important cause which showed be kept in mind. Smokers's polycythemia is an important entity causing CVT in patient cohort of Uttrakhand, high altitude causing chronic hypoxia may be multiplying the risk of polycythemia in these patients. This highlights the importance of smoking cessation as one of the treatment step for treating CVT in smoker's polycythemia.

Limitation of the study

It was a retrospective study and hypercoagulable work up could not be done in all the patients. Also work up for systemic inflammation diseases causing acquired hypercoagulable state such as Behecet's disease was not carried out. Twenty percent of Polycythemia Vera possess negative JAK2mutation.[30]

Despite the limitation of the study, it is conferred that smoking could be attributed as an important etiology for the secondary cerebral thrombosis causing headache. Therefore, the authors

would like to draw the attention to these unprecedented cases in light of higher rates of adverse outcome in undiagnosed cases.

CONCLUSION

Cigarette smoking has been associated with many medical problems, and one of these is polycythemia. This case series demonstrates a common but rarely correlated presentation of smoker's polycythemia. It stresses that cerebral thrombosis should be born in mind as initial presentation of headache in smokers. Early treatment can significantly reduce both morbidity and mortality in these patients. The patients should be followed up carefully by hematological and radiological investigations to establish the diagnosis and induce prompt treatment.

REFERENCES

1. Bousser MG, Cerebral venous thrombosis; nothing, heparin, or local thrombolysis? Stroke. 1999;30:481-3.
2. McAloon EJ, Streiff RR, Kitchens CS: Erythrocytosis associated with carboxyhemoglobinemia in smokers.South Med J. 1980;73:137–139.
3. McBane RD 2nd, Tafur A, Wysokinski WE: Acquired and congenital risk factors associated with cerebral venous sinus thrombosis. Thromb Res. 2010;126:81–87.
4. Landolfi R, Di Gennaro L, Falanga A: Thrombosis in myeloproliferative disorders: pathogenetic facts and speculation. Leukemia. 2008;22:2020–2028.
5. Barbui T, Carobbio A, Rambaldi A, Finazzi G: Perspectives on thrombosis in essential thrombocythemia and polycythemia vera: is leukocytosis a causative factor? Blood. 2009;114:759–763.
6. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, et al: Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood. 2007; 109:2446–2452.
7. Smith JR, Landaw SA: Smokers' polycythemia. N Engl J Med. 1978;298:6–10.
8. Kiss L.The role of Sándor Korányi and the HighTatras in unravelling the pathogenesis of altitude polyglobulia. Orv Hetil. 2008;149:1147-9.
9. Vicari AM, Ponzoni M, Alberetto M, Martani C, Pontiroli AE, Folli F. Erythrocytosis in a patient with chronic obstructive pulmonary disease. Haematologica. 1998;83: 183-6.
10. Bang SM, Lee JS, Ahn JY, Lee JH, Hyun MS, Kim BS, Park MR, Chi HS, Kim HY, Kim HJ, Lee MH, Kim H, Won JH, Yoon HJ, Oh DY, Nam EM, Bae SH, Kim BK; Korean MPN Working Party. Vascular events in Korean patients with myeloproliferative neoplasms and their relationship to JAK2 mutation. Thromb Haemost. 2009;101:547-51.
11. The Antiphospholipid Antibodies in Stroke Study (APASS) Group. Clinical, radiological and pathological aspects of cerebrovascular disease associated with antiphospholipid antibodies. Stroke. 1993;24 (suppl 1):120-3.
12. The International Classification of Headache Disorders, 3rd edition (beta version) 2013: Cephalalgia 33:629–808.
13. Krayenbuhl H. Cerebral venous and sinus thrombosis. Clin Neurosurg. 1967;14:1-24.
14. Bousser MG, Chiras J, Bories J, Castaigne P.Cerebral venous thrombosis. A review of 38 cases. Stroke. 1985;16: 199-213.
15. Ameri A, Bousser MG. Cerebral venous thrombosis. Neurol Clin. 1992;10:87-111.
16. Averback P. Primary cerebral venous thrombosis in young adults: the diverse manifestations of an under recognized disease. Ann Neurol. 1978;3:81-6.
17. McAloon EJ, Streiff RR, Kitchens CS: erythrocytosis associated with carboxyhemoglobinemia in smokers. South Med J. 1980;73:137–139.
18. Prchal JT: Primary and secondary polycythemias (erythrocytosis); in Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT (eds): Williams Hematology, ed 8. New York, McGraw-Hill, 2010;56:823–838.
19. Yoo JH, Park TS, Maeng HY, Sun YK, Kim YA, Kie JH, et al: JAK2 V617F/C618R mutation in a patient with polycythemia vera: a case study and review of the literature. Cancer Genet Cytogenet. 2009;189:43–47.
20. Smith JR, Landaw SA: Smokers' polycythemia. N Engl J Med. 1978;298:6–10.
21. Berlin NI: Diagnosis and classification of polycythemias. Semin Hematol. 1975;12:339.
22. Stuart BJ, Viera AJ: Polycythemia vera. Am Fam Physician. 2004;69:2139–2144.
23. Prchal JT: Primary and secondary polycythemias (erythrocytosis); in Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT (eds): Williams Hematology, ed 8. New York, McGraw-Hill. 2010;56:823– 838.
24. McBane RD 2nd, Tafur A, Wysokinski WE: Acquired and congenital risk factors associated with cerebral venous sinus thrombosis. Thromb Res. 2010;126:81–87.
25. Landolfi R, Di Gennaro L, Falanga A: Thrombosis in myeloproliferative disorders: pathogenetic facts and speculation. Leukemia. 2008;22:2020–2028.
26. Barbui T, Carobbio A, Rambaldi A, Finazzi G: Perspectives on thrombosis in essential thrombocythemia and polycythemia vera: is leukocytosis a causative factor? Blood. 2009;114:759–763.
27. Landolfi R, Di Gennaro L, Barbui T, De Stefano V, Finazzi G, Marfisi R, et al: Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood. 2007;109:2446–2452.
28. Ferro JM, Canhao P, Stam J, Bousser MG, Barinagarrementeria F, ISCVT Investigators: Prognosis of cerebral vein and dural sinus thrombosis: results of the international study on cerebral vein and dural sinus thrombosis (ISCVT). Stroke. 2004;35:664–670.
29. Kaplan JM, Biller J, Adams HP Jr. Outcome in Non septic spontaneous superior sagittal sinus thrombosis in adults: a 14-year experience. Cerebrovasc Dis. 1991;1:231-4.
30. Halpern JP, Morris JGL, Driscoll GL. Anticoagulants and cerebral venous thrombosis. Aust NZ J Med.1984;14:643-8.
31. Einhaupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. Lancet. 1991;338: 597-600.
32. Kaplan JM, Biller J, Adams HP Jr. Outcome in nonseptic spontaneous superior sagittal sinus thrombosis in adults: a 14-year experience. Cerebrovasc Dis. 1991;1:231-4.

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