Journal of Advances in Medicine and Medical Research

25(4): 1-9, 2018; Article no.JAMMR.38540
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

In-hospital Imaging Prevalence, Patterns of Neurological Involvement in Cerebral Venous Sinus Thrombosis: Analysis from Pakistan

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/38540
Editor(s):
(1) Jera Kruja, Neurology, University of Medicine, Tirana, Albania and Member of Scientific Committee, European Academy of Neurology Member of Teaching Courses Committee, World Federation of Neurology, Albania.
Reviewers:
(1) Adrià Arboix, University of Barcelona, Spain.
(2) Luis Rafael Moscote-Salazar, Universidad de Cartagena, Colombia.
(3) Predrag Džodić, University of Niš, Serbia.
Complete Peer review History: http://www.sciencedomain.org/review-history/23220

Original Research Article

Received 7th November 2017
Accepted 26th January 2018
Published 15th February 2018

ABSTRACT

Objective: The objective of the study was to calculate in-hospital imaging prevalence and report patterns of neurological involvement in cerebral venous sinus thrombosis patients presenting at a tertiary care hospital in a developing country.
Methods: A cross-sectional analytical study elicited data from the Department of Radiology at the Aga Khan University Hospital from January 2007 until December 2012. Patients of either sex were retrospectively recruited from medical record database. They were included if they presented with or were referred from clinical departments for evaluation of suspected cerebral venous sinus thrombosis. Diagnosis of cerebral venous sinus thrombosis was made on the basis of a combination of Magnetic resonance imaging with Magnetic resonance venogram imaging findings.
Results: A total of 597 scans were reviewed. Mean age was 37.46 ± SD 15.4 years, range: 72 years. Out of the total sample of 66, 28(46%) were males. Infarcts were more pronounced in females. Regarding clinical features, most commonly presenting symptom was a headache and weakness, 16 (26%) and 14 (23%) respectively. The 6 -year in-hospital imaging prevalence of cerebral venous sinus thrombosis was calculated as 11.055%, (66/597), 95% CI [8.54-13.56%]

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and true positive rate as 10.22%, (61/597), 95%CI [7.79-12.65%]). Patterns of sinus involvement were multi sinus involvement, and the major combination was superior sagittal, sigmoid and transverse 9(15%), sigmoid and transverse 8(13%), all sinuses 5 (8.2%).
Conclusion: There is increasing trend of multi sinus involvement in our population which can be detected early, by contrast, enhanced magnetic resonance venogram.

Keywords: Prevalence; cerebral thrombosis; neurological disorder; magnetic resonance imaging; confidence interval; Pakistan.

ABBREVIATIONS

ALL : Acute Lymphoblastic Leukemia
CT : Computed Tomography
CVST : Cerebro Vascular Sinus Thrombosis
FA : Flip Angle
FLAIR : Fluid-Attenuated Inversion-Recovery
FOV : Field of View
MRI : Magnetic Resonance Imaging
MRV : Magnetic Resonance Venogram
OCP : Oral Contraceptive Pill
3D : Three Dimensional
WI : Weighted Imaging

1. INTRODUCTION

Cerebral venous sinus thrombosis (CVST) occurs secondary to thrombosis of intracranial cerebral veins and dural sinuses. It hinders proper drainage of deoxygenated blood from brain resulting in drastic hemodynamic changes which can be fatal [1,2]. It is not uncommon in the South Asian subcontinent [3-7]; however, no multi-centre or multi-national registry is available to define the exact numbers [8], potential risk factors, patterns of involvement and outcomes [9]. However, few hospital-based studies have been conducted to elaborate these points [10-12]. Over the past decade, epidemiology of CVST has significantly changed and is not a rare disorder anymore [3-7]. CVST was first diagnosed by Ribes in 1825, who described thrombosis of dural venous sinuses on the autopsy of a man who suffered from seizures and delirium [13]. CVST accounts for 0.5% of all stroke cases. The estimated incidence of CVST between adult and pediatric populations differs notably. In adults, the incidence of CVST has been estimated to be 3–4 cases per million people, while the respective incidence in children and neonates is higher and reported as 7 cases per million [14]. In children, it is more prevalent in less than 6 months old [15] and the highest frequency in the adult age group is reported between 20-40 years. Seventy-five percent (75%) of the adult cases are women of childbearing age with potential risk factors of pregnancy, puerperium, and usage of oral contraceptives [14]. The signs and symptoms associated with CVST have a wide spectrum [16]. If the disease is undiagnosed and untreated in its early course, it can lead to increasing morbidity and mortality secondary to complications such as cerebral oedema, intracranial hypertension, cerebral ischemia, and hemorrhagic venous infarction [16]. Headache is the commonest reported symptom in patients with CVST. It is present in ninety percent of cases and reflects raised intracranial pressure [17]. According to largest clinical study (the ISCVT, including 624 patients), there is mostly single sinus involvement. The most commonly affected sinus is superior sagittal sinus (62%), followed by the transverse sinuses (41.2–44.7%), the straight sinus (18%), and the cavernous sinus (1.3%). Both superior sagittal and transverse sinuses are affected in 30% [10]. Timely diagnosis of CVST is of sheer importance as early anticoagulation is thought to prevent thrombus propagation. This in turn prevents fatal complications and long-term morbidity [18]. Diagnosing CVST often challenges the physicians, however owing to the new era of advanced imaging and use of contrast-enhanced magnetic resonance venography (CEMRV), early exclusion of CVST is now possible in no time [19]. More recently, the evolution of noninvasive diagnostic imaging methodologies such as CT venography and MR imaging, angiography, and venography have enhanced our awareness regarding the full clinical spectrum of CVST and facilitated with a more accurate estimation of its exact occurrence. Hence embarking prompt management with improved prognosis and outcome [18-20]. Table 1 depicts the comparison of previous literature based on incidence, prevalence of CVST patients.

2. METHODS

2.1 Patient Population and Data Collection

A cross-sectional analytical study was designed to elicit data from the Department of Radiology at

the Aga Khan University Hospital from January 2007 until December 2012. The data were retrospectively collected from October 2012 till December 2012. The study protocol was approved by the departmental research committee. Patients of either sex were retrospectively recruited from medical record database if they presented with or were referred from clinical departments for evaluation of suspected CVST. A non-probability convenience sampling technique was employed to recruit patients in the study after providing consent. Patients were excluded if their MRV was normal or contraindication to MR and claustrophobia.

2.2 Radiological Case Definition

Diagnosis of CVST was made on the basis of a combination of MRI with MRV findings, like loss of flow void on T2W images with filling defect (thrombus) in the sinus with enhancement of the wall appearing as empty delta sign.This was further confirmed by the partial or complete absence of filling of one Dural sinus on two projections on contrast-enhanced Magnetic Resonance Venogram (MRV) [21].

2.3 MR Protocol

Scans were performed on 1.5 Tesla Siemens Avanto with 6 channel head coil scanner. The data was collected in all patients using a 3 Dimensional (3D) contrast-enhanced MRV with 64 loss/slab,1 mm thick, a 512 x 192 matrix, FOV = 25.6 cm x 19.2 cm (512 x 256 matrix with in-plane phase FOV = 0.75), for an in-plane resolution of 0.5 mm x 1 mm. Other parameters were: flip angle FA=30, TE/TR =12.2/34 ms for an acquisition time AT = 5 min: sec. k-space data was saved and transferred for post-processing. Additional MRI sequences acquired included T2-weighted image (WI), Fluid-Attenuated Inversion-Recovery (FLAIR) and T1W. TWI both with and without a single dose intravenous bolus of 0.1 mMol/Kg Gd-DTPA 5 min after injection. First dynamic source images were acquired and then maximum intensity projection images were reformatted from source data.

2.4 MR Image Analysis Technique

All MRI and MRV examinations were initially reviewed by resident/Neuro-radiology fellow followed by a final reading of scans with consultant Neuro-radiologists having at least eight years of experience. Images were reviewed in conjunction with clinical history and were reviewed on PACS.

The images were analyzed for the presence or absence of thrombosis on conventional MRI as loss of T2 weighted flow void with delta sign on postcontrast scan. Dynamic scans were also reviewed along with 3D reformatted images.

2.5 Analytical Plan

Data were entered and analyzed on SPSS version 20.0. Mean ± SD was computed for a quantitative variable like age. Proportions were calculated for categorical variables like gender, clinical features. 6-year in-hospital imaging incidence and prevalence was calculated with 95% confidence intervals. True positive rate with 95% confidence intervals of CVST was also computed.

3. RESULTS

A total of 597 MRV were referred and reviewed in the department over a period of six years. Out of the total sample, 66 were diagnosed as positive CVST patients out of which 28(46%) were males. The mean age of the patients was 37.46 ± SD 15.4 years, range: 72 years, minimum 4, and maximum 76 years. Nearly half of the patients, 31(51%) were admitted in the ward, 23 (37%) presented in the Emergency and the rest were out-patient clinics 7(21%) with Neurology as the main referral. Out of the total, 29(48%) presented with an infarct and 3(5%) with subarachnoid haemorrhage (SAH). Infarcts were more pronounced in females. Regarding clinical features, most commonly presenting symptoms were a headache and weakness, 16 (26%) and 14 (23%) respectively. Seizures 6(9.8%) and fever 2(3%) were the least presented symptoms followed by vertigo 1(1%). There was no history available for 5 patients of the total sample. Majority of the patients did not present with any co-morbid state. Out of total 33 females, 10 (30%) were post-partum, 7(12%) were suffering from malignancy, 3(5%) with infection and one each presented with hypertension and congenital disease. Therefore, 29 (47%) presented with the only thrombosis without parenchymal abnormalities like SAH or infarct. The 6 -year in-hospital imaging prevalence [new and old cases] of CVST was calculated by 66/597 = 11.05%, 95% CI [8.54-13.56%]. The numerator denoted some number of positive CVST cases versus the denominator

which is the total MRV referred and performed over a period of six years in a tertiary care hospital setting in a developing country. Fig. 1A shows a trend of CVST patients over 6- year period at The Aga Khan University Hospital, Karachi, Pakistan. Fig. 1B further depicts the trend of CVST patients with respect to gender. We also computed the true positive rate of CVST as 10.22%, 95%CI [7.79-12.65%]. The pattern of sinus involvement was multi sinus involvement, the major combination was superior sagittal, sigmoid and transverse 9 (15%), sigmoid and transverse 8(13%), all sinuses 5 (8.2%) followed by transverse sinus, cortical vein, internal jugular vein, sigmoid sinus and vein of Galen. Fig. 2A shows single sinus involvement with associated parenchymal oedema in a female patient and Fig. 2B shows multi-sinus involvement without parenchymal involvement in a patient of leukemia.

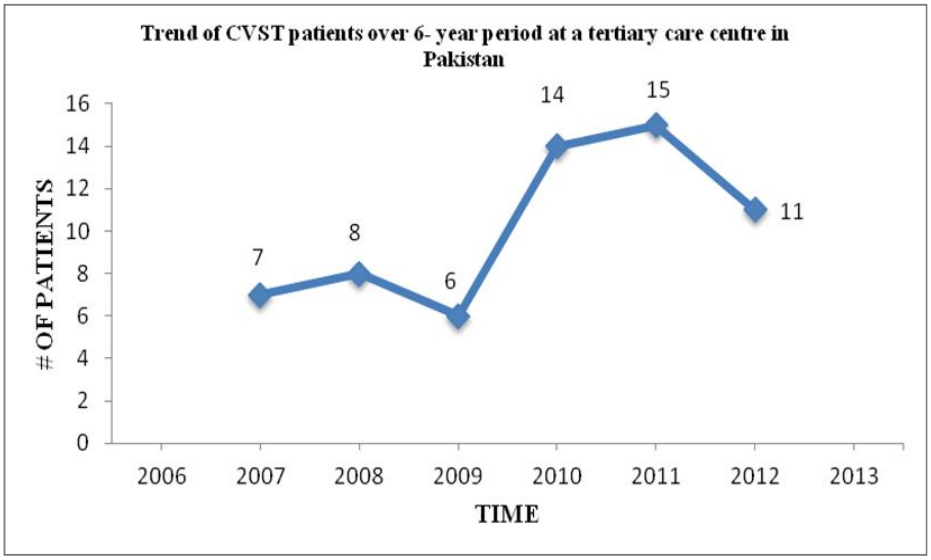

Fig. 1A. Trend of CVST patients over 6- year period at a tertiary care center in Pakistan

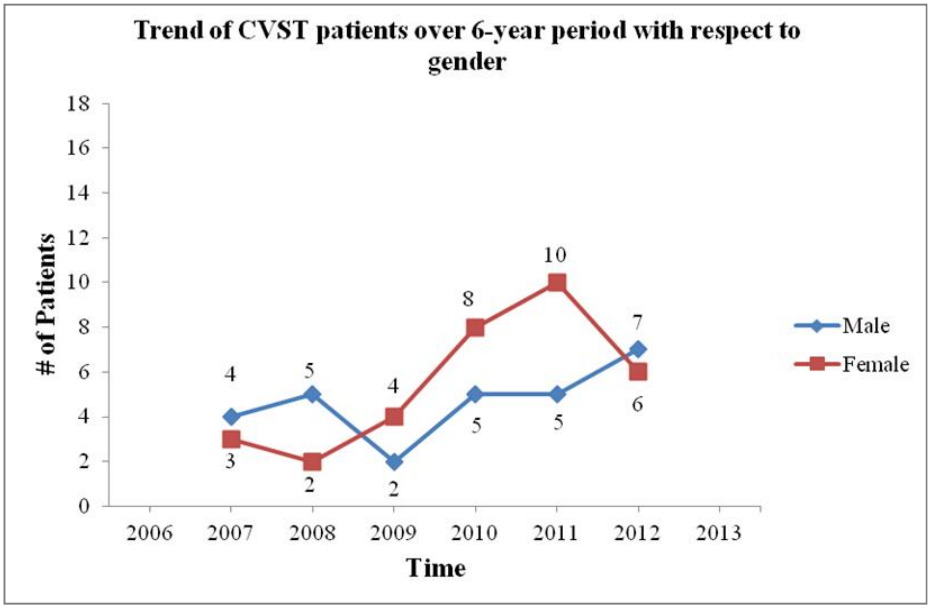

Fig. 1B. Trend of CVST patients with respect to gender over a period of 6 years at a tertiary care hospital in Pakistan

Table 1. Comparison of previous literature based on incidence/prevalence of CVST

S. no.	Author	Year	Country	Sample	Incidence/Prevalence
1	Daif A, et al.	1995	KSAŧ	40	7.0/100000
2	Ferro JM, et al.	2001	Portugal	142	0.22/1000000
3	de Verber G, et al.	2001	Canada	160	0.67/100000
4	Pillai LV, et al.	2005	India	62	10-20%
5	Janghorbani M, et al.	2008	Iran	465	12.3/million
6	Mubarak F, et al.*	2017	Pakistan	66	11.05%

ŧ Kingdom of Suadi Arabia
** Our study*

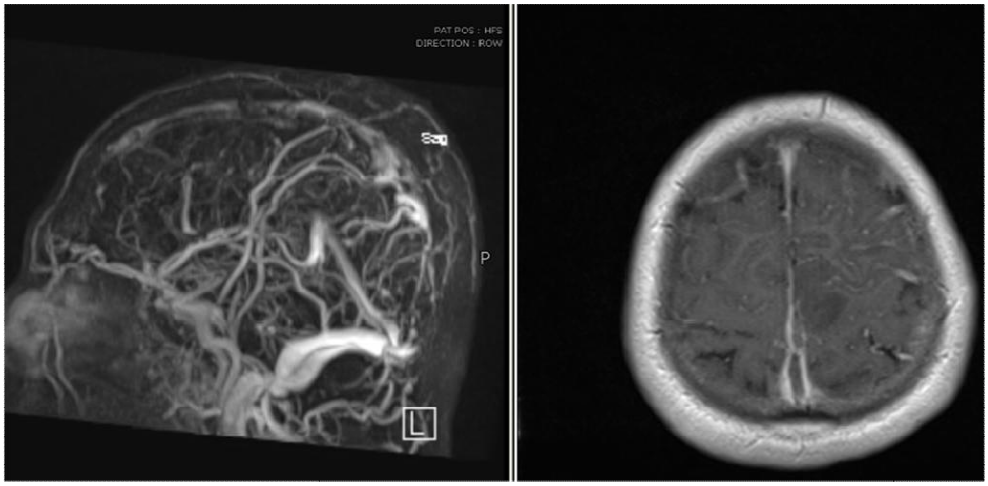

Fig. 2A. Post contrast 3D MRV and 2B. Post-contrast Axial
30 years female presented with headaches for four days, history of oral contraceptive use. Postcontrast axial shows filling defect in superior sagittal sinus with brain edema in the left medial frontal parietal lobe. Corresponding post contrast 3D MRV shows defects in superior sagittal sinus

Fig. 3. 3D Post contrast case MRV
60 years male diagnosed case of ALL presented with headache. Postcontrast 3D MRV shows occluded superior sagittal sinus in the anterior aspect, left transverse and sigmoid sinus

4. DISCUSSION

Previously cerebral venous sinus thrombosis was assumed to be a rare disease based on earlier evidences on its incidence and prevalence [22, 23]. It has been mostly reported on autopsy studies which have shown very low frequency [24-28] but at present it is now established that CVST is frequent as compared previously [3]. This may be because of better widespread use of neuroimaging and enhanced clinical attentiveness [29,30] that has helped in early diagnosis and management [31]. Nearly half a decade before, it was reported to be 1 per 2 million persons per year in England and Wales [32]. Bousser et al. [31] reported in 2007, that CVST affects about 5 people per million in the English population [33]. Ferro JM et al. [10] conducted the largest clinical series which recruited 630 patients over a 3 year period from 89 centers in 21 countries. Generalizability of their study results to patients of CVST from

Africa and Asia is indeterminate because insufficient representation of patients from these continents was observed. Daif et al. [3] observed 40 patients over a period of 9 years from two main hospitals of Saudi Arabia. He reported hospital frequency of 7 CVST cases per 100 000 patients and the incidence calculated was less than 1 per 100 000 populations per year [3]. Studies conducted in India have recruited large number of cases and further reported that 10-20% of young strokes are attributable to CVST [6] This paper aims to report in-hospital 6-year imaging prevalence and true positive rate of CVST as 11.05 %, 95%CI [8.54-13.56%] and 10.22%, 95%CI [7.79-12.65%] respectively. To our best knowledge, this is the first reported imaging prevalence from our part of the developing world. We calculated in-hospital prevalence of CVST as number of positive [new and old] CVST cases divided by the total MRV referred and performed over a period of six years in the department. The burden of CVST was denoted by 66 new and old diagnosed cases over a six-year period. The reported period prevalence is 11.05 %, 95%CI [8.54-13.56%] from our study. All ages and both sexes are affected, with a preponderance of women between 20 and 40 years of age, probably reflecting frequency of specific causes such as use of oral contraceptives, pregnancy and puerperium [34] With the advent and common use of neuroimaging, there is better diagnosis and prognosis of CVST in this era. CVST has a broad range of symptomatology and mimics many other neurological conditions such as stroke, meningitis, encephalopathy and benign intracranial hypertension. Headache is the most common symptom related to CVST and been reported in 80% of cases. This is followed by seizures, focal neurological deficits, altered consciousness, and papilloedema, which can present alone or in combination with other symptoms. Imaging therefore supports early diagnosis and intervention as clinical presentation in seclusion can be misleading [22]. Thrombosis of a specific cerebral venous channel is related to a particular clinical presentation and parenchymal changes and is helpful in localizing the affected area in brain. Cerebral venous infarction is related to cortical vein and superior sagittal vein thrombosis while cranial nerve palsy is a feature of cavernous sinus thrombosis. Lateral sinus occlusion can present as headache or pseudotumour cerebri and jugular foramen syndrome is secondary to jugular bulb involvement.

Last but not the least subarachnoid haemorrhage is an important presenting feature of CVST and can present as a thunderclap headache [26]. The patients' mean age in our study was similar to that of case series analysis conducted in Iran in 2011. They had a larger group of female patients but majority suffered from the hypercoagulable state related to OCPs which is quite similar to our cases who were mainly postpartum [35]. Our study reports that all ages and both sexes are affected, with a preponderance of women between 20 and 40 years of age, probably reflecting the frequency of specific causes such as the use of oral contraceptives, pregnancy and puerperium. A headache was the most common presenting symptom in our study which is comparable, though it was not associated with seizures; and papilledema was not studied as a symptom in our subjects. We also report the maximum involvement of superior sagittal sinus with or without the combination of lateral sinuses, which is again identical. The results of our study are also homologous to that of Khealani BA et al. since its target population belongs to Pakistan and the Middle East. He reported the mean age of 35.76 ± 13.15; range, 10–76 years. Majority of the cohort had a predisposing factor of infection followed by the post-partum state. A headache was the most common clinical feature and the majority of patients had thrombosis of the superior sagittal sinus [36]. Recently, a larger cohort of patients consisting of 428 patients was studied in India, in which men were mainly affected. Anemia, hyperhomocysteinemia, alcohol and OCP intake were the predisposing factors in descending frequency while the postpartum state was lower down the list. Hence showing reduced gender predilection for women. This variability in results can be explained on the basis of environmental and social differences among the two populations. It may also be attributable to a variety of difference in situation, methodology and sample size. A headache as the most common symptomatology and principal occlusion of superior sagittal sinus in this survey is equivalent to our results [37].

We adopted a cross-sectional analytical design, therefore, need to emphasize on several important shortcomings and benefits of a cross-sectional design**.** As data were retrospectively retrieved, we were totally dependent on the availability and accuracy of the medical record system. We utilized existing data that was recorded for reasons other than research. We are aware of an element of selection bias as the authors self-selected the cases. This is a single-

centre, hospital-based study which limits its scope as a truly representative sample of community population; thereby limiting its generalizability. The strength of this retrospective study review is that we managed to accumulate data for a relatively large number of patients who underwent imaging with clinical suspicion of CVST. This was an appropriate topic for a retrospective study because of limited resources. A prior stringent case definition was defined as quoted above. There are only few imaging positive cases [only 66 over a period of six years] and ours is one of the specialized tertiary care hospitals in the city for the imaging diagnosis of such patients. Our study has reported the in-hospital radiology imaging based incidence of CVST from our part of the world. We also reported trend analysis for CVST cases for a period of six years which is novel and reported for the first time.

4.1 Unanswered Questions and Future Directions for Research

We are unable to find the cause of multi-sinus involvement as the major contributor to our study population. We assume that CVST was missed in the initial phase when there might be single sinus involvement. In our study, there were few pregnant females in the first trimester who presented with a headache and they have not undergone post contrast MRV scan due to relative contraindication to Gadolinium. We anticipate that the negative rate of post-contrast MRV from all ordered scans predispose to underdiagnosed CVST or having unnecessary post-contrast studies for CVST. There is a need to select patients for post contrast MRV based on strong clinical suspicion. We also need to see other causes of a headache in such patients and tailor exam accordingly; this will save resources and scan time.

5. CONCLUSION

This particular study enforces to conclude that, imaging prevalence [new and old cases] of cerebral venous sinus thrombosis is 11.055 %, with 95% CI [8.54-13.56%] and amongst which true positive rate is 10.22 %, with 95% CI [7.79-12.65%]) amongst the total population assessment of hospital imaging prevalence nearly about of 6 years. Major combination of neurological involvement was CVST with associated parenchymal abnormalities and the major combination was found in the superior sagittal, sigmoid and transverse sinuses.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical permission has been collected and preserved by the authors.

DISCLAIMER

This study was presented as the poster in Conference of Radiological Society of North America, 27 November - 2 December 2016.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/23220