Predictors of Late Seizures in Patients with Cerebral Venous Sinus Thrombosis: A Retrospective Analysis

Sir,

Cerebral venous sinus thrombosis (CVST) is a subtype of stroke with extremely varied clinical presentations and imaging findings, and it has good outcomes in the majority. The annual incidence of CVST is approximately 2–5 cases per million per year population.[1] It typically occurs in young adults.[2] It has been reported that up to 44.3% of patients may have seizures in the early stage of the disease, and 9.5% of patients may have late seizures.[3] Seizures secondary to CVST are categorized into early/acute symptomatic (within 14 days after the diagnosis) and late/remote symptomatic seizures (beyond 14 days after diagnosis).[4] In a study by Ferro *et al*.,[3] late seizures were more frequent in CVST patients with early symptomatic seizure and hemorrhagic infarct. In another study by Sánchez van Kammen *et al.*,[5] early seizure, intracerebral hemorrhage, subdural hematoma, and decompressive hemicraniectomy were found to be predictors of late seizures. However, there is no clear consensus on the validity of these predictors. In the present study, we tried to find the predictors of late seizures in patients with CVST, based on clinical, imaging, and biochemical variables.

We conducted a retrospective, cross-sectional, single center, hospital-based study. The hospital registry was screened retrospectively to identify records with a diagnosis of acute CVST from July 2019 to January 2013. Fifty consecutive patients diagnosed with acute CVST and available for follow-up to a minimum of 1 yearin each subgroup i.e., a) without seizures, b) with only early seizures, and c) with late seizures were included in the study [Figure 1]. Patients with seizures secondary to antiseizure medications (ASMs) withdrawal, alcohol withdrawal seizures, and patients with a history of seizures in the past were excluded from the study.

The demographic and clinical characteristics and imaging features of these three subgroups are described in the table [Tables 1 and 2]. The median (IQR) age for the late seizure subgroup was 35 (27.7–47.2) years, the early seizure subgroup was 36 (27.544.0) years, and for the no seizure subgroup was 34 (27.5–40.2) years. The gender ratio (M:F) in the late, early, and no seizure subgroups were 21:29, 19:31, and 29:21, respectively. Forty-six (92%) of 50 patients with late seizure were on ASMs, of which 30 (65%) patients were on single ASMs only. The median duration of first late seizure recurrence was 8.5 (4–18.25) months. During a median (IQR) follow-up duration of 22 (12–30) months, 12 (24%) of 50 patients had more than one episode of late seizure. Late-recurrence of seizures were more commonly found in patients with a motor deficit ($\chi^2 = 8.067$, $P = 0.018$) and language dysfunction ($\chi^2 = 7.197$, $P = 0.027$) at presentation. On imaging, hemorrhagic infarct ($\chi^2 = 10.69$, $P = 0.005$), involvement of frontal lobe ($\chi^2 = 29.91$, $P < 0.001$), raised intracranial pressure, and cortical vein thrombosis ($\chi^2 = 11.67$, $P = 0.003$) were found to be significantly associated with late seizures as per the univariate analysis. The risk factor in the form of alcohol consumption ($\chi^2 = 10.16$, $P = 0.001$) was also found to be significantly associated with late seizures [Table 1]. Multinomial regression analysis was done to analyze the data. The deviance Chi-square test suggested that the model was fit for data analysis. Regression analysis showed that the patients with frontal lobe involvement ($P = 0.044$) and hemorrhagic stroke ($P = 0.002$) were more likely to be associated with late seizures in comparison to the patient with no seizure group. While in comparison to the early and late seizure group, cortical vein involvement and frontal lobe involvement were more likely

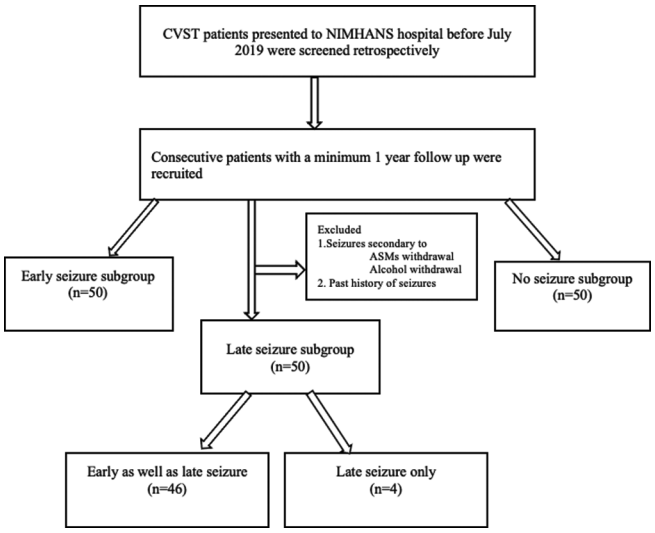

Figure 1: Flowchart for patient selection

Table 1: Demographic, baseline clinical profile, laboratory investigation of patients

	Late seizure recurrence group ($n=50$)	Early seizure only group ($n=50$)	No seizure group ($n=50$)	χ^2	P
Age (Median)(IQR)	35 (27.7–47.2)	36 (27.5-44.0)	34 (27.5-40.2)	2.008	0.366*
Sex (F: M)	21:29	19:31	29:21	4.509	0.105
Clinical feature					
Duration of symptoms (days)	6.38±5.4	6.22±4.76	7.52±5.61		0.313*
Headache	46/50 (92%)	45/50 (90%)	46/50 (92%)		1.000†
Altered sensorium	16/50 (32%)	16/50 (32%)	14/50 (28%)	1.029	0.598
Language dysfunction	8/50 (16%)	10/50 (20%)	9/50 (18%)	7.197	0.027
Motor deficit	28/50 (56%)	22/50 (44%)	14/50 (28%)	8.067	0.018
Isolated raised ICT feature	11/50 (22%)	22/50 (48%)	19/50 (40%)	3.047	0.080
Isolated parenchymal features	31/50 (62%)	23/50 (46%)	16/50 (32%)	9.032	0.002
Both raised ICT and parenchymal features	37/50 (74%)	42/50 (84%)	34/50 (68%)	0.437	0.508
Investigation					
Anaemia	21/50 (42%)	13/50 (26%)	21/50 (42%)	3.034	0.219
Polycythaemia	10/50 (20%)	8/50 (16%)	5/50 (10%)	2.400	0.301
Hyperhomocysteinemia	24/50 (48%)	32/50 (64%)	25/50 (50%)	3.382	0.184
Low vitamin B12	18/50 (36%)	17/50 (34%)	17/50 (34%)	1.152	0.562
ANA/ANCA	3/31 (9%)	5/29 (17%)	2/35 (6%)		
APLA	0/32 (0%)	0/21 (0%)	3/34 (9%)		
Protein C	5/12 (42%)	1/10 (10%)	2/7 (28%)		
Protein S	6/11 (54%)	3/9 (33%)	3/7 (42%)		
Antithrombin III	1/7 (14%)	3/8 (38%)	1/7 (14%)		
Alcohol consumption	14/50 (28%)	24/50 (48%)	10/50 (20%)	10.16	0.006
Smoking	7/50 (14%)	10/50 (20%)	5/50 (10%)	2.083	0.353
Postpartum state	7/21 (33%)	2/19 (10%)	4/29 (14%)	2.710	0.099
Pregnancy	0/21 (0%)	0/19 (0%)	3/29 (10%)		
Menstrual disturbance with OCP inatke	6/21 (29%)	5/19 (26%)	4/29 (14%)	1.662	0.197

* Kruskal-Wallis Test; † Fisher's Exact Test; Abbreviations: IQR: Interquartile range, ICP- intracerebral pressure

Table 2: Imaging features of patients

	Late seizure recurrence group ($n=50$)	Early seizure only group ($n=50$)	No seizure group ($n=50$)	χ^2	P
Sinus involved					
Superior sagittal	45/50 (90%)	43/50 (86%)	33/50 (66%)	7.588	0.230
Cortical vein	37/50 (74%)	25/50 (50%)	22/50 (44%)	11.67	0.003
Transverse	32/50 (64%)	36/50 (72%)	35/50 (70%)	0.805	0.668
Sigmoid	28/50 (56%)	34/50 (68%)	36/50 (72%)	3.061	0.216
Multiple sinuses	34/50 (68%)	37/50 (74%)	38/50 (76%)	0.793	0.372
Deep venous sinuses	5/50 (10%)	7/50 (14%)	10/50 (20%)	2.204	0.363
Infarct characteristics					
Non-haemorrhagic Infarct	8/50 (16%)	11/50 (22%)	3/50 (6%)	5.220	0.074
Haemorrhagic infarct	40/50 (80%)	30/50 (60%)	26/50 (52%)	10.69	0.005
Without parenchymal lesion	2/50 (4%)	9/50 (18%)	21/50 (42%)	20.384	<0.001
Lobe involvement					
Frontal	38/50 (76%)	18/50 (36%)	12/50 (24%)	29.91	0.001
Parietal	15/50 (30%)	19/50 (38%)	14/50 (28%)	1.287	0.526
Temporal	8/50 (16%)	13/50 (26%)	17/50 (34%)	4.300	0.116
Midline shift	30/50 (60%)	18/50 (36%)	20/50 (40%)	6.553	0.038
Raised ICP sign	38/50 (76%)	43/50 (86%)	34/50 (68%)	3.516	0.172
Subdural hematoma	1/50 (2%)	4/50 (8%)	3/50 (6%)	1.848	0.396
Decompression surgery	13/48 (27%)	5/41 (12%)	10/29 (34%)	5.165	0.075

Table 3: Comparison with previous studies

Studies	Predictors of late seizures	The median duration of follow up in months
Ferro *et al*., 2003[3]	Early symptomatic seizure and hemorrhagic infarct	18 months
Davoudi *et al*., 2013[5]	Acute seizure and supratentorial parenchymal lesion	27 months
Kammen *et al*., 2020[5]	Early seizure, intracerebral hemorrhage, subdural hematoma, and decompressive hemicraniectomy	24 months
Current study	Frontal lobe involvement, cortical vein involvement, and hemorrhagic infarct	22 months

to be associated with late seizures. The correct classification percentage of the fitted model is 68% (Supplementary data).

Seizures and epilepsy can influence the management and outcome of CVST, both in the acute stage as well as in follow-up. The appropriate and rational use of ASMs is essential for better outcomes. Predictors of seizure occurrence in early and late phases CVST will help the clinicians to decide on initiation as well as the duration of treatment with ASMs. Multiple large cohort studies have shown that the presence of focal deficits, hemorrhagic infarct, the involvement of frontal lobe, and superior sagittal sinus was significantly associated with the occurrence of early seizures in patients with CVST.[6-9] However, much less is known about predictors of late seizures. Hence, the present study aimed at determining the predictive factors for late seizures in patients with CVST. On multinomial regression analysis, frontal lobe involvement and hemorrhagic infarct were significantly associated with late seizures when compared with the "no seizures" group. This is the first time we are proposing the involvement of the frontal lobe in patients with CVST as a predictor for late seizures, which needs to be confirmed in prospective studies. The hemorrhagic infarct and cortical involvement are found to be associated with late seizure in other stroke types.[10] The subdural hematoma and decompression surgery were not found to be significantly associated with the late seizures in the current study. In this study, of 50 patients with late seizures, 46 (92%) patients had early seizures as well suggesting it as a predictor for late seizures, but the prevalence of late seizures in the early seizures subgroup has not been studied. Other studies attempted to determine the predictors of late seizures were compared [Table 3]. The late seizures as well as the duration of ASMs in patients CVST can have a negative impact on the physical and mental health of patients, especially in women of childbearing age and their families. In this study, 32% of the patients had a seizure after 1-year symptom onset, whereas 12% of patients had seizure recurrence even after 2 years of symptom onset. The finding highlights that one should have a cautious approach while tapering ASM, especially when the patient has above described predictors of late seizures.

The strengths of the study were that it was a single center study with a relatively uniform treatment protocol and follow-up. The limitations of our study are the following: 1) retrospective data, 2) small sample size, and 3) full panel of investigations were not available uniformly for all patients. This might justify the

need of a prospective study to determine the exact predictors for late seizures.

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Conflicts of interest

There are no conflicts of interest.

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