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CRITICAL REVIEW AND INVITED COMMENTARY

Seizure in cerebral venous and sinus thrombosis

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Epilepsia Open, 3(3):316–322, 2018
doi: 10.1002/epi4.12229

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Summary

Many conflicting issues exist about seizure in the setting of cerebral venous and sinus thrombosis (CVST). In this article we aimed to address the existing data regarding incidence, characteristics, predictors, treatment, and prognosis of acute and late seizures in patients with CVST and to prepare more practical information for clinicians. PubMed, Embase, Web of science and Cochrane databases were searched within 1966–2016 using relevant keywords. A total of 63 papers met the inclusion criteria. Seizures are classified as acute symptomatic seizures (ASS; first 14 days) and post-CVST epilepsy (PCE; after 14 days). The incidence had been reported in a wide range of 6.9–76% for ASS and 4–16% for PCE. Focal and generalized seizures were observed with different predominance. ASS commonly occurred in patients with loss of consciousness, focal neurological deficits, supratentorial lesions and thrombosis in superior sagittal sinus, straight sinus, and cortical veins. PCE had been predisposed by occurrence of ASS, motor deficit, and supratentorial lesions, particularly hemorrhage. Most experts believe that primary prophylaxis with antiepileptic drugs in the acute phase is not indicated. However, the initiation of prophylaxis after the first seizure in patients with supratentorial lesions or focal neurological deficit should be recommended. The quality of current evidence is low and most conclusions are based on expert opinions. More accurate reports of seizure semiology, detailed antiepileptic treatment plans, and outcomes are necessary to answer the existing questions.

KEY WORDS: **Seizure, Cerebral venous thrombosis, Treatment, Prognosis.**

Although the first reports of cerebral venous and sinus thrombosis (CVST) were published in the 19th century,[1–3] the best approach to manage these patients and prevent the probable sequels is still a matter of debate. In comparison to arterial stroke, focal and generalized seizures are more commonly seen in CVST and have been known as presenting symptoms of disease since the first reports.[4–6] Acute symptomatic seizures (ASS) occur in about 35–50% of all patients, with a higher incidence (76%) in peripartum CVST.[7–10] Moreover post-CVST epilepsy (PCE) remained a troublesome sequel that might affect quality of life and needs long-term treatment with antiepileptic drugs (AEDs).[4]

Many factors have been postulated to predict acute phase and late-onset seizures, and to influence the decision of clinicians to start and continue treatment with AEDs.[11–16] However, there is still a great deal of disagreement about the treatment of CVST-induced seizures. Primary prophylactic antiepileptic treatment has been suggested by a few studies.[17] Other reports have recommended initiation of treatment after one or two seizures in the acute phase in patients with specific findings on neurological examination and neuroimaging.[18–22] Data regarding duration of treatment and the best type and dosage of AEDs in the acute phase are also controversial.[13,23,24] The level of evidence is low, and no powerful well-designed randomized controlled trial has targeted these issues.[25]

In this review we aimed to collect the existing data about incidence, semiology, and characteristics of seizures in CVST. We also discussed the predictive factors of early and late-onset seizures, their treatment, and prognosis.

Accepted May 7, 2018.

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Key Points

- Seizures are common consequences of cerebral venous and sinus thrombosis
- Acute symptomatic seizures frequently associate with focal neurological deficits and supratentorial lesions
- Post-CVST epilepsy has a strong correlation with history of acute symptomatic seizures
- Despite the lack of solid evidence, prophylactic treatment after first acute symptomatic seizure is recommended under certain circumstances

Methods

Data sources and search strategy

We performed a comprehensive search of the published literature from 1966–2016 using PubMed, Embase, Web of science, and Cochrane databases. The keywords included the following MESH and free terms: (1) CVT, (2) CVST, (3) CST (4), Cortical vein thrombosis, (5) Cerebral venous sinus thrombosis, and (6) Dural sinus thrombosis. We combined each of 6 words with the terms: (1) seizure, (2) epilepsy, (3) antiepileptic drugs, and (4) treatment.

Study selection

All abstracts were reviewed and assessed for relevance. In addition, we manually reviewed the references of relevant studies. The selected abstracts underwent full-text review to determine if they met following inclusion criteria: (1) Researches in adult humans (>16 years); (2) English language; (3) report of 10 or more patients; (4) presentation of data regarding incidence, characteristics, predictors, treatment, or prognosis of seizure in CVST.

Publications in other languages were considered only if they had an English abstract with adequate information. The studies that did not meet the criteria were excluded. We also considered review articles if they could provide more additional data. Figure 1 explains the full data-gathering process.

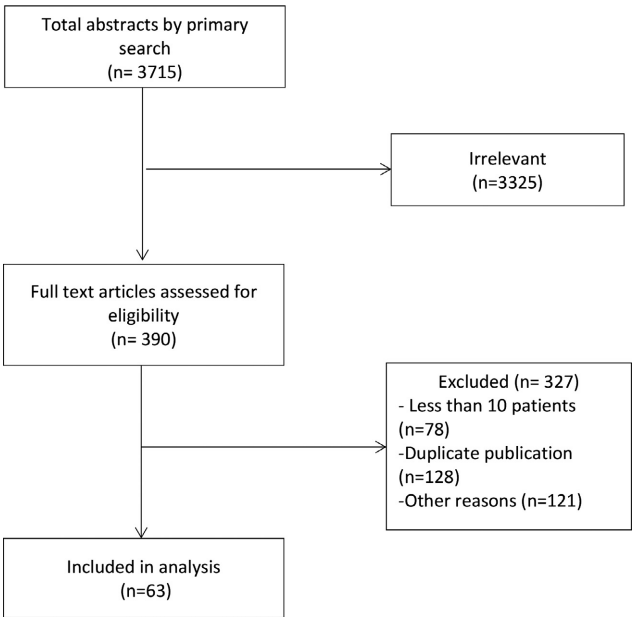

Figure 1.
Flowchart of study selection.
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Discussion

Definition and incidence

Different timing methods have been used to classify seizure occurrence during the course of CVST. The most accurate classification is referred to Ferro et al.,[10] who assorted seizures into 3 groups including presenting seizures (before diagnosis of CVST), early seizures (within 14 days of diagnosis of CVST), and late seizures (after 14 days of diagnosis of CVST). But most of the studies have used the terms "acute" for both presenting and early seizures and "remote" for late seizures. According to recent definitions and terminology of seizure and epilepsy, in this review we have used the term "acute symptomatic seizures" (ASS) to address seizures within first 14 days of diagnosis and "post-CVST epilepsy" (PCE) to mention later seizures.[26,27]

The incidence rate of ASS has a widely varied range in different studies. ASS in CVST are reported in 6.9–76% of patients, with the higher incidence in severe CVST cases (60%) and peripartum CVST (76%).[13,28–58] The risk of PCE is low compared with the high rate of ASS, and is reported in about 4–16% of patients in different studies that followed patients between 12 months to a mean of 77.8 months.[11–13,28,44,54,59] Based on the results of the international study on cerebral vein and dural sinus thrombosis (ISCVT), 11% of the patients experienced PCE (36 patients by 6 months, 55 by 1 year, and 66 by 2 years).[32] Although the follow-up periods are different and in some studies unreliable ways of data gathering have been used that makes it difficult to draw an exclusive conclusion, there is a consensus on occurrence of most of PCE cases within the first year.[11,13,60]

Seizure type and semiology

None of the reviewed studies investigated the relation between semiologic features of seizures and location of parenchymal lesions or venous system thrombosis.

In some studies the only[13] or the prominent type[54,61] of seizures was focal with or without secondary generalization.

Epilepsia partialis continua (EPC) has also been reported as a clinical manifestation of seizures.[62] Masuhr et al.[22] in 2004 described Todd's paresis following seizures caused by CVST and introduced it as an indicator of CVST in the relevant setting, particularly if paresis switches between both

sides. In his next study at 2006, Todd's paresis has been reported in 54.7% of patients following ASS.[13]

However, in other studies, generalized seizures are reported to have a higher frequency,[16,24,40] particularly in severe cases of CVST who underwent thrombolysis.[46]

It is difficult to determine which type of seizures is more common due to controversial existing data. The other problem that causes concern about the reliability of the reported incidence of generalized seizures is the possible lack of close supervision at the time of seizure occurrence, which may cause unwanted neglect of brief focal semiology at onset.

Predictors of ASS

To provide a better understanding of the predictors of seizures in CVST, we classified them based on demographic factors, associated symptoms and signs, anatomical location, imaging findings, laboratory data, and treatment options.

Demographic factors

Age has no predictive role in ASS.[13,14] In a study by Ferro et al.[63] on CVST in the elderly, no difference regarding type (focal or generalized) and incidence of seizures was observed between young or middle-aged patients (<65 years) and elderly patients (≥65 years), either in the acute phase or follow-up. In addition, gender has no predictive value in seizure occurrence.[13,14,54,64]

Symptoms and signs

In a study by Mahale et al.[24] on predictors of ASS in CVST, altered mental status, Glasgow coma scale (GCS) score <8, and paresis had a meaningful association with ASS, whereas headache, vomiting, aphasia, sensory symptoms, and papilledema did not. The association of motor deficit with ASS is also confirmed by other studies,[13,16,40,65] but in contrast to the Mahale study, aphasia was a predictor of ASS, in ISCVT,[16] and in the VENOPORT study ASS were associated with sensory deficits.[10] Conversely, the risk of early seizures in patients presenting with isolated intracranial hypertension is low (<3%)[16] and the comparison of patients with and without headache as a presenting symptom has shown that seizures are significantly more common in patients without headache (58% vs. 32%).[66] It can be obviously concluded that involvement of brain parenchyma at or near the motor cortex leading to motor or sensory deficit predisposes patients to ASS. However, the isolated intracranial hypertension, at least before causing loss of consciousness, has no role in this regard.

Anatomic involvement and imaging

ASS are more commonly reported in patients with supratentorial lesions,[10,16,40,54] particularly of the frontal[24,40,54,65] and parietal lobes.[40,54] Davoudi et al.[40] stated that lesions limited to one lobe were significantly associated with ASS, whereas involvement of more than one lobe showed no association.

Although in a retrospective multicenter study by Terazzi et al.[61] and another study by Davoudi et al.,[40] seizure occurrence had no correlation to location of venous thrombosis, most studies reported that thrombosis of straight sinus[16] and superior sagittal sinus[16,24,57] are significantly associated with ASS. In addition, there are multiple reports of significant association between ASS and cortical vein thrombosis.[13,15,16,67]

In contrast, patients with seizures had significantly less involvement of transverse and superficial sinuses.[24] Damak et al., in their 9-year cohort study, compared 62 patients with isolated lateral sinus thrombosis and 133 with involvement of other parts of the cerebral venous system. They reported that seizures were significantly less frequent in isolated lateral sinus thrombosis than in other patients with CVST (16% vs. 47%).[68]

Considering neuroimaging, ASS are more frequent in patients with focal edema, or ischemic or hemorrhagic infarcts.[13,24,40,54,69] In cortical vein thrombosis, close contact of cortical veins to the cerebral cortex can cause local alterations of the blood–brain barrier and trigger seizures.[13] In addition, occlusion of the superior sagittal sinus and cortical veins, which drain venous blood from motor and sensory cortices, could increase the risk of seizures due to motor cortex damage.[16] If hemorrhage occurs, focal cortical irritation caused by blood metabolites could also predispose acute seizures.[70,71]

Etiology

Although Kalita et al.[72] have found no role for underlying cause in predisposition for seizures; there are reports of possible effect of etiology. In a study by Davoudi et al.,[40] thrombophilia and a history of miscarriage were more common in patients with ASS. Evidence about pregnancy is more controversial. In some studies, CVST during pregnancy or the puerperal period was associated with a high incidence of seizures,[16,73–75] whereas others did not find the same results.[8] Possible predisposing factors for occurrence of seizures in this group of patients are reported as young age and concurrence of preeclampsia and fasting.[73–76]

Lab

The only laboratory data that has associated significantly with ASS was high D-dimer levels.[24] No data regarding the effect of other biochemical parameters on occurrence of seizures exist.

Treatment

Heparin therapy and time to start anticoagulant had no effect on the occurrence of ASS in CVST.[13] In addition, no statistically significant difference has been reported between the incidence of ASS in patients who received unfractionated or low molecular weight heparin.[77]

Predictors of PCE

Etiology

The only underlying cause mentioned in the literature to associate with a higher risk of PCE is thrombophilia.[40]

Symptoms and signs

Similar to ASS, paresis is reported as a risk factor of PCE,[59] but no association of focal neurological signs other than motor deficit has been found. In the study by Davoudi et al.,[40] loss of consciousness at presentation was significantly associated with PCE but such a relation has not been confirmed by other studies. ASS have a close association with development of PCE in patients with CVST[11,40,59,60] and should be considered as a strong predictor.

Anatomical involvement and imaging

Supratentorial lesions are associated with late recurrence of seizures.[40,72] In the study by Davoudi et al.[40] sigmoid sinus thrombosis and lesions in the occipital, temporal, and parietal lobes had a significant association with PCE. Such a relation between the involved lobe and PCE has not been reported by others.[72] Presence of hemorrhage on admission imaging is considered as a risk factor for PCE as well.[11,48,59]

Treatment

As it is indicated by Price et al.,[25] there is no well-designed randomized controlled trial regarding primary or secondary prevention of seizures in CVST and also there is no solid evidence to prove the effectiveness of prophylactic use of AEDs for prevention of seizures. Thus the decision-making regarding time, type, dosage, and duration of antiepileptic treatment in patients with CVST is often individualized. In a study by Coutinho et al.,[78] the authors investigated expert opinions about treatment of CVST by invitation of corresponding authors of related papers during a 5-year period. They reported large practice variations regarding the use of prophylactic AEDs. The results indicated that 8% of experts initiate prophylactic AED in all patients, 21% prescribe prophylactic therapy only in patients with focal cerebral lesions, and the others (71%) did not recommend prophylaxis ($p < 0.001$).

There is low quality evidence about the effectiveness of prophylactic use of AEDs after first seizure in patients with CVST. But those authors who advocate this approach recommend prophylactic treatment because of the high incidence of seizures in CVST and the possibility of recurrence of seizures and status epilepticus in acute phase that might lead to deterioration of metabolic state and cause rise of intracranial pressure or even early death.[17] However, most researchers restrict the use of AEDs to patients with seizures under certain circumstances.[31] Prophylactic treatment recommended by these authors is limited to patients with supratentorial lesions such as edema, infarction, or hemorrhage on neuroimaging. Some studies particularly focused on the presence of hemorrhage and cortical vein thrombosis on imaging and focal motor and sensory deficits on neurological examination as indicators of a necessity to start prophylactic treatment.[11,13,16,17,19–22,39,60,79–82] Despite all controversies, based on current data, prophylactic treatment with AEDs has no place in patients without focal neurologic deficits or supratentorial lesions, and might be harmful in these cases,[31] as mentioned in the European Stroke Organization/European Academy of Neurology (ESO/EAN)[83] and American Heart association/American Stroke Association (AHA/ASA) guidelines.[80] Again, despite the lack of sufficient data, AHA/ASA guidelines suggested that in patients with CVST and no supratentorial lesion or focal neurological deficits who experience a seizure, early initiation of AEDs for a defined period is probably recommended to prevent further seizures,[80] whereas ESO/EAN guidelines presented no recommendations for these patients. Initiation of antiepileptic therapy only in patients who experienced repetitive seizures during the acute phase has fewer advocates.[44]

There is no consensus regarding the most appropriate type and dosage of AEDs.[13,23,24,84] It seems reasonable that similar to the treatment approach for seizures accompanying a comorbidity, the best option is to select an AED with fewer drug interactions. When indicated, injectable forms of levetiracetam, lacosamide, and probably sodium valproate should be considered to prevent further seizures in the acute phase. However, for long-term treatment, levetiracetam, lamotrigine, and gabapentin are more appropriate options.

Moreover, no consensus exists about the duration of treatment. Whereas PCE is more common in patients with ASS and commonly occurs within the first 6–12 months after the acute stage, treatment with AED for 1 year is recommended for patients with ASS and previously indicated risk factors.[11,12,21,31,32] However, in patients without these risk factors who have received AED therapy, gradual taper of AEDs after the acute stage seems reasonable.[31] The approximate duration of 3 months could be considered for these patients[13]; however, if seizures recurred during or after drug tapering, continuation of antiepileptic treatment for another 1–2 years or more is recommended.[44] It is noteworthy that treatment with AEDs in the acute phase has no role in the prevention of PCE; therefore according to ESO/EAN guidelines, no recommendations can be made for prevention of PCE at the current time.[83]

Effect of seizures on CVST prognosis

Information about the effect of seizures on CVST prognosis is conflicting. Some studies have reported higher functional disability[16,50,51] and mortality[16,76,85,86] in patients with seizures. In a study by Stolz et al.,[43] patients with more than 2 seizures despite treatment with AEDs had a significantly higher in-hospital mortality rate. Similarly, in the

study by Masuhr et al., occurrence of fewer than 3 seizures caused no significant difference regarding mortality. In this study, mortality rate was 3 times higher in patients with status epilepticus.[13]

In most of the other studies seizure was not associated with a worse outcome.[24,28,32,40,87,88] Neither seizure nor status epilepticus had an effect on in-hospital mortality[72,89,90] or 6-month outcome.[69,72]

Two other studies have reported positive prognostic effect of seizures in CVST. In a study by Korathanakhun et al.,[45] seizure predicted the lower incidence of dependency or death, and in a study by Stam et al. on outcome of thrombolytic therapy in severe cases of CVST, seizures occurred less frequently in the fatal cases than in surviving patients. However, because altered mental status was among the inclusion criteria of the study and it could occur as a part of postictal phase in patients with less severe disease, the authors suggested the possibility of wrong selection of patients that led to this result.[30]

There is no doubt that acute seizure is a warning symptom that might lead the clinicians to a more rapid diagnosis of CVST. These seizures more commonly occur in patients with structural lesions and motor deficits, which both could accompany long-term functional disability independent of seizure occurrence. The recurrence of seizures might be a sign of a more severe and diffuse process that not only involved multiple parts of the venous and sinus system but also caused severe edema, infarct, hemorrhage, or increase in intracranial pressure. Current data indicated that except for death instances that occur directly after seizures, in other severe cases, seizures are more likely a concomitant phenomenon rather than the etiology of functional disability or mortality. However, the adverse effects of PCE on a patient's independence and quality of life cannot be overlooked.

Conclusion

The current literature data on seizure in CVST is full of disagreements. The observational findings about the semiology and localization of seizure-onset zone are imperfect. Predictors of seizure occurrence that play a significant role in determining the need for treatment are controversial and in the most important part, treatment, which causes a remarkable effect on seizure control and prognosis, no competent randomized clinical trial exist. It seems that there is an urgent need for conducting of clinical studies with the target of seizure in CVST, particularly the management issue.

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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