Recanalisation and Outcome in Cerebral Venous-sinus Thrombosis

Cerebral venous thrombosis is an important treatable condition seen in neurological practice. It has a varied clinical presentation which may be difficult to recognise, leading to underdiagnosis.\(^1\) Unlike arterial lesions, venous sinus thrombosis involves many sinuses simultaneously often with minimal signs and become symptomatic when anastomotic veins are blocked.\(^2\) Symptoms and signs do not always correlate with sinuses involved nor on their recanalisation. In this issue Jain RS, Sripadma PV and Tejaswi S have published the article ‘Clinical characteristics, etiology, recanalisation and outcome in CVT’.\(^3\)

Despite the progress made in the last years, significant gaps persist in the understanding of the pathophysiology of brain damage and the mechanisms underlying the benefit of the available treatment strategies. Although there are several anecdotal reports of tissue recovery after recanalisation, particularly following endovascular treatment, the association between early venous recanalisation and tissue fate was not established until recently. A prospective cohort study found that patients with persistent venous occlusion by day 8 after starting of therapeutic anticoagulation treatment were more likely to have early worsening of non-haemorrhagic brain lesions.\(^4\) Besides suggesting that vessel recanalisation is relevant for the evolution of brain damage, this finding raises the hypothesis that anticoagulation-induced early partial recanalisation contributes to the clinical improvement often seen in these patients just a few days after treatment starts. Contrary to what is described in ischemic stroke, lesions showing diffusion restriction were fully reversible in most cases, particularly in patients achieving early venous recanalisation.\(^4\) This suggests that, in CVT, what was thought to represent cytotoxic oedema can still represent viable brain tissue, and may imply that a longer time window for treatment options exists in CVT, even in patients showing the so-called venous infarction.

In patients on anticoagulation, venous recanalisation is seen on follow up in 85%.\(^5\)

Recanalisation continues to occur in the first few months after CVT, although the process may take up to a year. A recent meta-analysis of patients with CVT on anticoagulation has shown an association between lack of recanalisation and worse functional outcome.\(^5\) Recanalisation was associated with a 3.3 fold increase in the odds of complete functional recovery. However, there is a lack of information on the temporal profile of recanalisation in these studies, thereby preventing any conclusion regarding a critical time window for venous recanalisation. There is scant evidence on whether persistent occlusion increases the risk of recurrence of CVT. However, such an association has been found in paediatric patients.\(^6\)

A study showed that recanalisation starts early in patients receiving therapeutic anticoagulation, as three quarters of patients had no persistent venous occlusion at day 8.\(^4\) However, venous recanalisation progresses with time, and complete recanalisation was only reached in about half of the patients at 90 days. Younger age was a predictor of early recanalisation and there was a trend to an increased rate of early recanalisation in patients showing the susceptibility vessel sign at admission.\(^4\) Although an association between persistent venous occlusion and worse functional outcome was found in the meta-analysis of previous cohort studies,\(^5\) that was not confirmed in this prospective cohort study with serial imaging at specific time points.\(^4\) Even so, the most severe presentations were underrepresented and the sample size was unpowere to detect an association with long-term functional outcome, in a disease that most often has a favourable prognosis, as measured by the Rankin scale.

There have been additions to the evidence base on the therapeutic side as well.

In the RE-SPECT CVT trial, the risk of recurrent venous thrombotic events was low in both arms, with similar rates of bleeding, suggesting that both dabigatran and warfarin may be safe and effective for preventing recurrent thrombotic events in patients with CVT.\(^7\) There are ongoing trials assessing the safety and efficacy of rivoroxaban in the treatment of CVT.

Oral anticoagulation after the acute phase of CVT contributes to the prevention of further venous thrombotic events, including recurrence of CVT. However, there have been no randomised controlled trials or prospective controlled studies assessing optimal duration of oral anticoagulation in this setting.\(^8\) The first trial that addresses this question (Extending Oral Anticoagulant treatment after acute Cerebral Vein Thrombosis, EXCOA-CVT) is currently ongoing.\(^9\)

Endovascular acute treatment of CVT remains an unproven therapy. The US guidelines recommend consideration of endovascular therapy for all patients who are comatose, deteriorate in spite of anticoagulation, and who do not have a parenchymal lesion with mass effect\(^10,11\) Due to the low quality of evidence, the European guidelines do not make any recommendation on usage of endovascular therapy and suggest not using it when there is a pre-treatment low risk of poor outcome.\(^8\)

A systematic review of case series of more than 3 CVT cases treated with mechanical thrombectomy, 40% of who had encephalopathy, reported a mortality of 14%, with worsening or new intracranial haemorrhage in 9%, complete recanalisation in 69%, and complete recovery in 35%. Chemical thrombolysis
in conjunction with mechanical thrombectomy did not result in additional harm or benefit, compared with other techniques.[12] However, no firm conclusions on the efficacy and safety of thrombectomy can be inferred in the absence of a control group.

Two studies provided evidence against the use of endovascular thrombectomy or thrombolysis in acute CVT. The randomised controlled trial of thrombolysis or anticoagulation for severe acute CVT (TO‑ACT)[12,13] was terminated prematurely for futility. Of the 67 randomised patients, no difference in clinical outcome was detected between those allocated to anticoagulation and endovascular treatment. In an evaluation of the Nationwide Inpatient Sample 2004–2014, patients receiving endovascular treatment experienced higher mortality (OR 1.96) after adjusting for age and CVT related complications.[14]

In the recent future, trials on endovascular thrombolysis/ thrombectomy, newer anticoagulants and duration of anticoagulants will help us increase the level of evidence for treatment recommendations for CVT.

D. Nagaraja
Director-DIMHANS and Director and Vice Chancellor, National Institute of Former Mental Health and Neurosciences (NIMHANS)-Deemed University, Bangalore, Karnataka, India

Address for correspondence: Dr. D. Nagaraja, Director-DIMHANS & Former Director and Vice Chancellor, National Institute of Mental Health and Neurosciences (NIMHANS)-Deemed University, Bangalore - 560 029, Karnataka, India. E-mail: dr.dnagaraja@gmail.com

REFERENCES
1. Ferro JM, Canhão P. Cerebral venous thrombosis. Presse Med 2016;45:e429-50.
2. Nagaraja D. Brain veins and their diseases. In: Toole JF, editor. Cerebrovascular disorders. New York: Lippincott Williams and Wilkins; 2004. p. 481-506.
3. Jain RS, Sripadma PV, Tejwani S. Clinical Characteristics, Etiology, Recanalization Rates and Neurological Outcomes in CVT: A Prospective Cohort Study. Ann Indian Acad Neurol 2022;25:229-34.
4. Aguiar de Sousa D, Lucas Neto L, Arauž A, Sousa AL, Gabriel D, Correia M, et al. Early recanalization in patients with cerebral venous thrombosis treated with anticoagulation. Stroke 2020;51:1174-81.
5. Aguiar de Sousa D, Lucas Neto L, Canhão P, Ferro JM. Recanalization in cerebral venous thrombosis. Stroke 2018;49:1828-35.
6. Kenet G, Kirkham F, Niederstadt T, Heinecke A, Saunders D, Stoll M, et al. Risk factors for recurrent venous thromboembolism in the European collaborative paediatric database on cerebral venous thrombosis: A multicentre cohort study. Lancet Neurol 2007;6: 595-603.
7. Ferro JM, Coutinho JM, Dentai F, Kobayashi A, Alasheev A, Canhão P, et al. Safety and efficacy of dabigatran etexilate vs dose adjusted warfarin in patients with cerebral venous thrombosis: A randomized clinical trial. JAMA Neurol 2019;76:1457-65.
8. Ferro JM, Bousser MG, Canhão P, Coutinho JM, Crassard I, Dentai F, et al. European Stroke Organization guideline for the diagnosis and treatment of cerebral venous thrombosis-endorsed by the European Academy of Neurology. Eur J Neurol 2017;24:1203-13.
9. Miranda B, Aaron S, Arauž A, Barinagarrementeria F, Borhane-Haghghi A, Carvalho M, et al. The benefit of EXTending oral antICOAgulation treatment (EXCOA) after acute cerebral vein thrombosis (CVT): EXCOA-CVT cluster randomized trial protocol. Int J Stroke 2018;13:771-4.
10. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, et al. Systematic review of 185 cases. Stroke 2015;46:1263‑8.
11. Miranda B, Aaron S, Arauž A, Barinagarrementeria F, Borhane-Haghghi A, Carvalho M, et al. The benefit of EXTending oral antICOAgulation treatment (EXCOA) after acute cerebral vein thrombosis (CVT): EXCOA-CVT cluster randomized trial protocol. Int J Stroke 2018;13:771-4.
12. Siddiqui FM, Dandapat S, Banerjee C, Zuurbier SM, Johnson M, Stam J, et al. Mechanical thrombectomy in cerebral venous thrombosis: Systematic review of 185 cases. Stroke 2015;46:1263-8.
13. Coutinho JM, Ferro JM, Zuurbier SM, Mink MS, Canhão P, Crassard I, et al. Thrombolysis or anticoagulation for cerebral venous thrombosis: Rationale and design of the TO‑ACT trial. Int J Stroke 2013;8:44-50.
14. Siddiqui FM, Weber MW, Dandapat S, Scaife S, Buherkempe M, Ortega-Gutierrez S, et al. Endovascular thrombolysis or thrombectomy for cerebral venous thrombosis: Study of Nationwide Inpatient Sample 2004–2014. J Stroke Cerebrovasc Dis 2019;28:1440-7.

Submitted: 02-Nov-2021  Accepted: 03-Nov-2021  Published: 01-Mar-2022

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

DOI: 10.4103/aian.aian_957_21