

# Pearls & Oy-sters: Delayed progression of isolated cortical vein thrombosis despite therapeutic INR

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## Pearls

- Isolated cortical vein thrombosis (ICVT) is a rare entity and diagnosis requires high clinical suspicion and select imaging modalities.
- Anticoagulation is the standard of care for ICVT treatment in the acute and chronic phases, but the specific choice of anticoagulation may be different for each case.

## Oy-sters

- When changing anticoagulants, enhanced clinical vigilance is recommended as delayed deterioration may occur.
- Patients may experience warfarin inefficacy, i.e., recurrent thromboembolism despite adequate dosing and an international normalized ratio (INR) within goal range.

A 23-year-old right-handed woman presented to a tertiary care emergency department with a 2-day history of a persistent, dull, right frontal headache after aerobic exercise. The morning of admission she experienced 2 episodes of involuntary right arm tonic-clonic movements, each lasting less than 1 minute. She did not lose consciousness. The second episode was followed by a right facial droop, as well as weakness and paresthesias of the right arm, which prompted her presentation to our facility.

Her medical history included catamenial migraine without aura. She denied alcohol, tobacco, and drug use. Her only medication was an estrogen-based oral contraceptive pill (OCP).

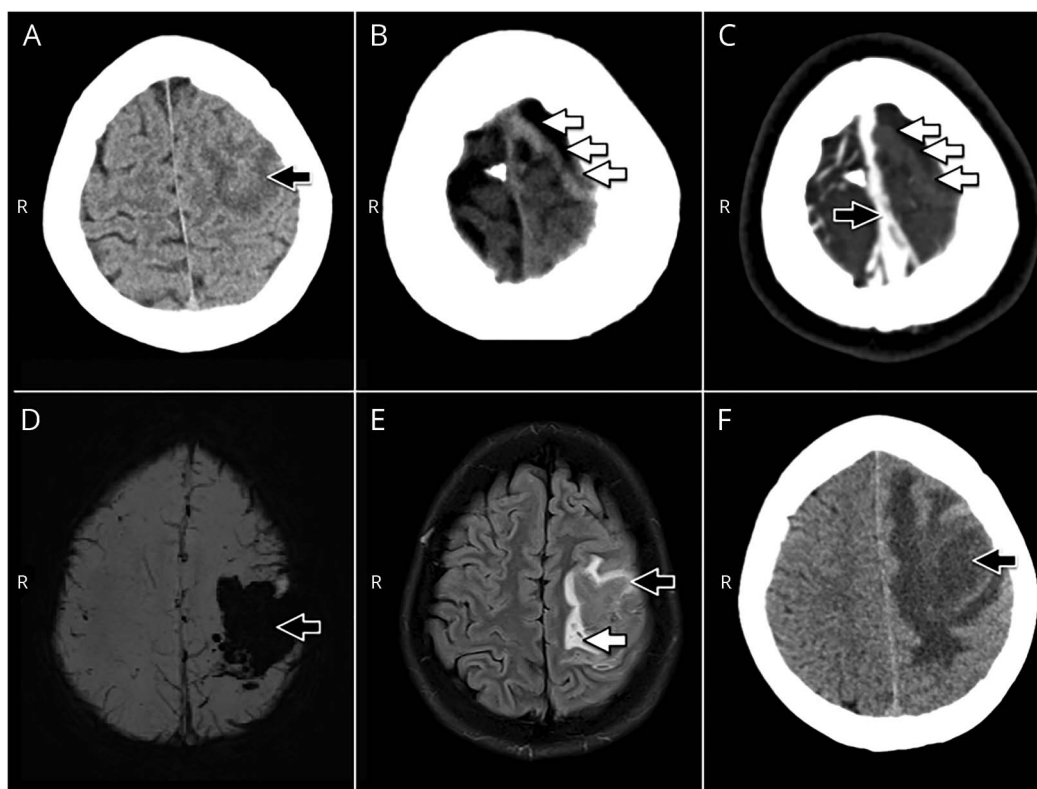
Upon arrival, she was afebrile with normal vital signs. Neurologic examination showed expressive aphasia and mild dysarthria. There was slight flattening of the right nasolabial fold. Strength was 4/5 in her proximal right upper extremity, 1/5 at the wrist, and 0/5 at the fingers. Laboratory studies showed mild thrombocytopenia (platelet count  $496 \times 10^3/\mu\text{L}$ ), but complete blood count, basic metabolic panel, prothrombin time/INR, and partial thromboplastin time were within normal limits. Urine drug and pregnancy screens were negative.

A brain CT scan revealed a venous infarct with surrounding edema in the left frontal convexity (figure, A) and a hyperdense serpiginous vessel in the left frontal lobe consistent with a thrombosed cortical vein (“cord” sign) (figure, B). CT venogram confirmed a thrombosed cortical vein (figure, C). The remainder of the venous system was patent.

The patient was admitted to the neurosurgical intensive care unit (ICU). Digital subtraction angiography (DSA) confirmed the diagnosis of ICVT and excluded other vascular pathologies. Hemorrhagic infraction was also seen on susceptibility-weighted imaging (SWI) (figure, D), and fluid-attenuated inversion recovery confirmed hemorrhage with minimal surrounding edema (figure, E).

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(A) Axial noncontrast CT scan of the brain shows the venous infarct with surrounding edema (arrow) in the left frontal convexity. (B) Axial noncontrast CT shows curvilinear increased density within a cortical vein denoting thrombosis (cord sign) (white arrows). (C) Axial CT venogram image at the same level as B shows the cortical vein does not opacify with contrast (white arrows) as opposed to the superior sagittal sinus (black arrow), confirming thrombosis. (D) Axial susceptibility-weighted image and (E) fluid-attenuated inversion recovery sequences confirm the large area of hemorrhagic infarct (black arrows). There is minimal surrounding edema (white arrow). (F) Noncontrast CT scan 12 days after discharge shows increased edema (arrow).

A hypercoagulable workup including lupus anticoagulant, homocysteine, thrombin time, antithrombin activity, prothrombin mutation, factor V Leiden, anticardiolipin antibodies, and protein S were unremarkable. Protein C activity was initially checked while the patient was taking warfarin, causing a low level. Platelets, elevated on admission, normalized thereafter. A CT scan of the chest, abdomen, and pelvis showed no evidence of malignancy.

Treatment was initiated with unfractionated heparin (UFH) on day 1 and followed by low molecular weight heparin (LMWH) bridged to warfarin with a goal INR of 2–3. For cerebral edema, a short course of dexamethasone was given. OCPs were discontinued. Physical and occupational therapy were consulted. The patient’s headache and examination gradually improved. She was discharged to acute rehabilitation with a therapeutic INR on hospital day 8.

During the patient’s 12th day of rehabilitation, she developed a progressive throbbing bifrontotemporal headache with photophobia and phonophobia. She had bilateral papilledema. Otherwise her neurologic examination remained stable. Her INR had remained therapeutic since discharge. A CT scan showed progression of the venous infarction and worsening edema

resulting in mass effect and midline shift (figure, F). MRI and magnetic resonance venography (MRV) showed a new left frontal ICVT. Dural sinuses remained patent. She was readmitted to the neurosurgical ICU. Noting progression of ICVT despite a therapeutic INR, warfarin was discontinued and LMWH started. Henceforth, her symptoms gradually improved and she was discharged back to acute rehabilitation. Protein C activity was normal several weeks after stopping warfarin. A follow-up CT head at 4 weeks postdischarge showed gradual resolution of the venous infarct.

### Discussion

ICVT is a rare entity caused by the thrombosis of one or more cerebral cortical veins without occlusion of the dural venous sinuses or the deep cerebral veins. ICVT is distinct from cerebral venous and sinus thrombosis (CVST), which involves the dural sinuses or deep cerebral veins.<sup>1</sup> Here we review the clinical features, diagnosis, and management of ICVT, and postulate why our patient worsened despite appropriate treatment.

Both CVST and ICVT primarily affect young women, which may in part be explained by sex-specific risk factors such as OCP use and pregnancy. Patients with ICVT rarely have

increased intracranial pressure, explaining a lower frequency of headache and papilledema when compared to CVST.<sup>2</sup> Parenchymal brain lesions (venous ischemic or hemorrhagic infarcts or vasogenic edema) are more common in ICVT than CVST, upholding the theory that venous infarcts are related to thrombosis of cortical veins rather than the venous sinuses.<sup>3</sup>

Diagnosis of ICVT requires imaging. CT, although not sensitive or specific, may show a cord sign indicating a thrombosed vein, as seen in our patient (figure, A). MRI and MRV are the preferred modalities for visualizing CVST; however, MRV may not reliably identify ICVT due to the size and anatomic variability of cortical veins.<sup>4</sup> CT venography is similarly limited but may show a filling defect with a hypodensity corresponding to the hyperdense cord sign on CT. Due to the ferromagnetic properties of blood degradation products, T1 and T2 images may take 5 days or more to detect a thrombus. In contrast, SWI demonstrate early thrombus as a distinct hypointensity in a tubular configuration.<sup>5</sup> These changes on SWI and gradient recalled echo may still be present years after onset, making determination of thrombus age impossible. Diffusion-weighted imaging findings of hyperintense clot signal and clot susceptibility signal may be useful if more sensitive sequences are unavailable.<sup>6</sup> DSA may be helpful when other studies are inadequate and can exclude other vascular pathology, such as arteriovenous malformations and fistulas. The figure, E, shows the greater sensitivity of SWI in detection of blood products in the area of venous infarct relative to that of the noncontrast CT scan of the brain (figure, A). The discrepancy in detection of blood may partly be related to the time lapse of 48 hours between the 2 imaging modalities and the blooming artifact in SWI that is known to slightly overestimate the hemorrhage volume.

Despite a low level of evidence due to the lack of large randomized controlled trials, anticoagulation is the cornerstone of acute and long-term treatment for CVST, and this has been logically extrapolated to ICVT. The International Study of Cerebral Vein and Dural Sinus Thrombosis (ISCVT) found that as compared to those treated with UFH, patients treated with LMWH were more likely to be functionally independent at 6 months and had fewer new intracerebral hemorrhages. UFH has long been used as the first line of therapy in the acute setting in order to reach therapeutic levels more quickly than with LMWH. However, this rarely happens, as it often takes more than 24 hours to reach desired levels. Other advantages of LMWH include a longer plasma half-life with a more stable therapeutic effect and lower risk for heparin-induced thrombocytopenia.<sup>4</sup> Another treatment option to consider is the off-label use of novel oral anticoagulants (NOAC). Although no randomized controlled trials using NOAC exist for CVST or ICVT, their favorable treatment profile for multiple other indications, such as deep venous thrombosis and pulmonary embolism, gives hope that they may be safe and effective for patients with CVST/ICVT. Further studies are needed.

Both CVST and ICVT generally respond well to anticoagulation and favorable outcomes have been reported,

although data are scarce for the latter.<sup>2,7</sup> One retrospective study showed venous infarcts and hyperintensity on diffusion-weighted imaging were predictors of clinical deterioration for patients with CVST. No mention was made of the timing of deterioration other than to say it occurred during the initial hospitalization.<sup>7</sup> Data from the ISCVT, in which 17% of patients had cortical vein thrombosis (unknown if isolated), showed that among patients presenting with isolated headache, those diagnosed within 7 days of symptom onset were more likely to experience neurologic worsening than those diagnosed after 7 days.<sup>8</sup> Whether this can be extrapolated to ICVT is unknown. Overall, the majority of in-hospital clinical and radiographic deterioration is reported to occur within the first 24–48 hours, which may in part be related to lack of therapeutic anticoagulation levels in those treated with UFH despite treatment.<sup>9</sup> Otherwise, delayed deterioration by weeks or months despite proper therapy is unusual and has not been reported previously in the literature. To our knowledge, this is the first report of a recurrent ICVT accompanied by clinical deterioration, 3 weeks after initial presentation, while on guideline recommended therapy.<sup>4</sup>

It is well-established that upon initiation of warfarin, a transient prothrombotic state occurs due to decreased vitamin K–dependent procoagulants including protein C levels. The prothrombotic state later resolves upon reaching therapeutic anticoagulation as measured by target INR levels, at which point the heparin bridging is stopped. Recurrent thromboembolism, despite an apparently adequate dose of warfarin and an INR within the recommended range, has been reported as warfarin inefficacy in the literature. The term is different from warfarin resistance, whereby a therapeutic INR is not achieved despite adequate dosing of warfarin, and the possible etiologies include pharmacokinetic (reduced absorption or increased elimination) or pharmacodynamics causes (excess vitamin K intake, hyperlipidemia, or hereditary conditions). Warfarin inefficacy has been described in patients with underlying cancer or HIV, but the majority of reported cases are cryptogenic.<sup>10</sup>

We present a case of delayed recurrent ICVT despite adequate anticoagulation and therapeutic INR levels in a young woman without any underlying thrombophilia or malignancy. We argue for close clinical and radiographic monitoring of patients undergoing changes in anticoagulation regimen with special consideration given to the possibility of warfarin inefficacy. This may be done on an outpatient basis for stable patients; however, patients experiencing a clinical decline must be evaluated emergently.

### Author contributions

Paul Gadiant: manuscript concept, data collection, research, drafting and revising manuscript for intellectual content. Dimitri Archer: research and drafting for intellectual content. Negar Asdaghi: manuscript concept, data collection, research, drafting and revising manuscript for intellectual content.

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## Disclosure

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