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## Reversal of restricted diffusion in cerebral venous thrombosis: case report

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**Abstract** We report a patient with extensive cerebral venous thrombosis who showed complete reversal of restricted diffusion on MRI, accompanied by excellent clinical recovery. The implications of these findings in relation to interpretation of diffusion changes in cerebral venous thrombosis are discussed, and differences with arterial stroke are highlighted.

**Keywords** Intracranial sinus thrombosis · Diffusion-weighted imaging · Cerebral infarct

### Introduction

Diffusion sensitive MR techniques have revolutionized imaging of stroke. In contrast to arterial stroke, however, the evolution of diffusion abnormalities in venous thrombosis and infarction is less well understood. We present a patient with extensive cerebral venous thrombosis leading to loss of consciousness and seizures. Following treatment there was complete reversal of restricted diffusion initially seen on MRI, accompanied by excellent clinical recovery. We discuss the implications of these abnormalities, and highlight the need for better understanding of the relationship between diffusion changes and pathophysiology of cerebral venous thrombosis.

### Case report

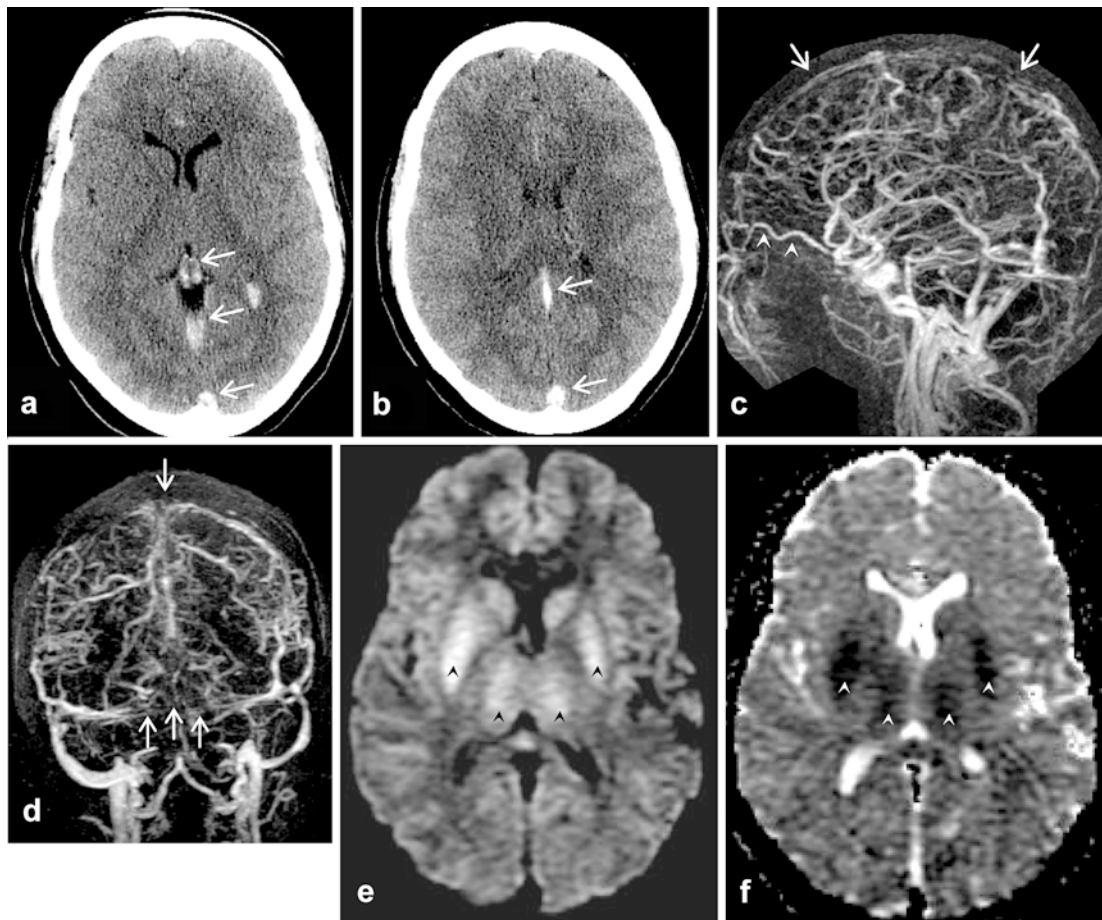
A 23-year-old woman presented with a 5-day history of increasing bifrontal headaches, followed by nausea and vomiting for 2 days. She had started taking oral contraceptives 1 month prior to presentation. There was no known prior illness or history of recurrent headaches. CT showed high density along the superior and inferior sagittal and straight sinuses and vein of Galen, indicating extensive dural sinus and deep vein thrombosis (Fig 1a, b). Intravenous heparin was initiated.

On arrival at our institution the patient had an episode of tonic-clonic seizures, treated with phenytoin. She was in a postictal state at the initial examination. Heparin was continued and she underwent MRI the next day which included contrast-enhanced auto-triggered elliptic centric-ordered venography [1], which revealed more extensive venous thrombosis (Fig 1c, d). In addition to the sites identified on CT, there was involvement of the internal cerebral veins, torcular and transverse sinuses. The petrosal sinuses and right superior ophthalmic vein were dilated, indicating alternative channels of venous drainage.

On diffusion weighted imaging (DWI) there were areas of high signal in the lentiform and caudate nuclei, thalami, left frontal and parietal and right parietotemporal regions. There were corresponding dark areas on the apparent diffusion coefficient (ADC) maps, indicating restricted diffusion (Fig 1e, f). No hemorrhage was seen on CT in these sites. The patient steadily recovered on heparin, with a gradually increasing level of consciousness. Neurological examination was normal on the fifth day of therapy. She was discharged on warfarin.

On follow-up visits she had no headache or neurological deficits and returned to all former activities. Her only complaint was mild difficulty in word-finding, which was not noticeable to her family members, who described her speech as normal. Investigations revealed no factors predisposing to cerebral venous thrombosis.

MR at 10 weeks showed patency of the dural sinuses except for a residual filling defect in the superior sagittal sinus (Fig 2a, b). DWI and ADC maps showed complete resolution of restricted diffusion (Fig 2c, d). The areas of involvement showed no residual signal change on MRI.



**Fig. 1a–f** Initial studies. **a, b** CT shows high-density thrombus in the internal cerebral veins, vein of Galen, straight and superior sagittal sinuses (*arrows*). **c, d** Contrast-enhanced MR venogram shows absent flow in superior and inferior sagittal sinuses, torcular and transverse sinuses, in addition to the sites of thrombus on CT. A dilated superior ophthalmic vein (*arrowheads*) provides collateral venous outflow. **e** Diffusion-weighted imaging (DWI) shows high signal in basal ganglia and thalamus bilaterally. **f** Map of apparent diffusion coefficients (ADC) shows these areas as dark, indicating restricted diffusion

## Discussion

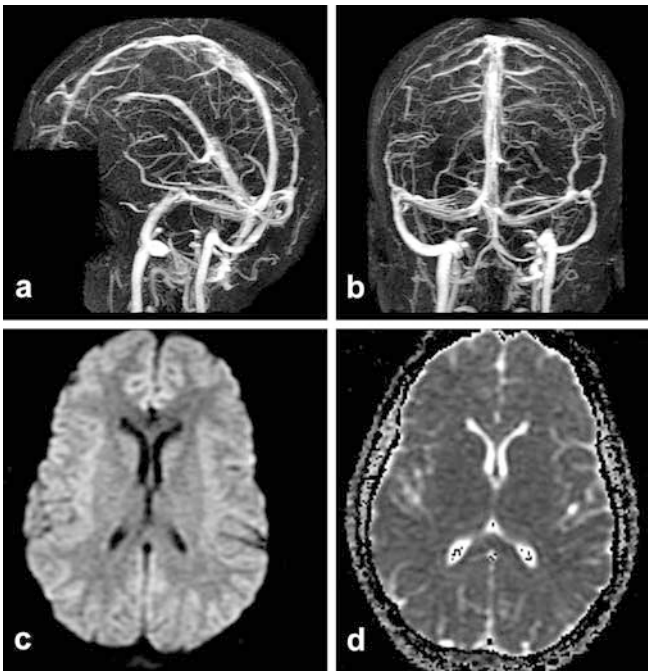
Cerebral venous thrombosis (CVT) has multiple causes, often related to hereditary or acquired predispositions [2], including hypercoagulable states such as oral contraceptive use. Presentation is variable and initial symptoms and signs are nonspecific. However, slow, stepwise progression, starting with headaches and vomiting and leading to neurological deficits and seizures is often seen [2].

MRI is now used for detection of CVT. Contrast-enhanced MR venography, such as we used [1], has obviated conventional angiography for diagnosing the

condition or defining its extent. DWI is routinely added to MRI investigation of CVT to identify cytotoxic edema and venous infarcts, as in arterial stroke.

The concepts underlying tissue water diffusion and its role in stroke have been of interest since the introduction of DWI. The latter allows assessment of molecular motion of water in biological tissues. This led to a major advance in ischemic stroke imaging when it was observed that restricted water movement occurred. DWI shows water proton diffusion, that occurs freely in the extracellular compartment, but is relatively restricted within cells. Shifting of water molecules from extra- to intracellular compartments and their subsequent intracellular restriction is thought to be responsible for ischemia-related abnormalities on DWI, believed to represent cytotoxic edema [3, 4, 5, 6, 7, 8].

In arterial stroke cytotoxic edema is caused by failure of ATP-dependent ion transport of sodium and calcium across the cell membrane. With rapid accumulation of sodium in ischemic cells, water follows to maintain osmotic equilibrium. Acute cytotoxic edema may be reversible if reperfusion occurs, as in animal models [9, 10] and also reported in humans after thrombolysis [11]. However, in most clinical situations, cytotoxic edema



**Fig. 2a–d** Imaging after treatment. **a, b** MR venogram shows patency of dural sinuses and deep cerebral veins (cf Fig 1c, d). **c, d** DWI and ADC map show complete reversal of restricted diffusion seen earlier (Fig 1e, f)

quickly progresses to cell death and necrosis. Restriction of diffusion, as seen on ADC maps, is claimed to be irreversible, and is taken to represent the infarcted zone in arterial stroke.

Data on the time-course of DWI changes and infarction in CVT are limited to case reports and small series. Vasogenic edema is commonly seen, but so are areas of reduced ADC, suggesting cytotoxic edema [7, 12]. Vasogenic edema, with normal or increased ADC, was the most common finding in 14 patients with confirmed CVT. However, low ADC suggesting cytotoxic edema was also often seen [13].

In another series of nine patients it was concluded that the pattern of DWI/ADC brain lesions in CVT is more heterogeneous than previously thought [14]. ADC were increased in five patients and decreased in three; one patient showed reduction in ADC to a degree usually reported with arterial infarcts, but the changes later resolved almost completely.

Reversal of “cytotoxic edema” in a case of CVT has been reported following endovascular thrombolysis [15]. Another report mentions marked resolution of diffusion and clinical abnormalities following intravenous heparin, though the findings refer to trace images and not ADC maps [16].

Interpretation and prognostic value of reduced ADC suggesting “cytotoxic edema” in CVT do not necessarily parallel those of arterial stroke, as demonstrated

by our patient and other reported cases. Concepts applying to arterial infarcts may not be applicable to CVT. Venous thrombosis is a slower process compared to the sudden drop in perfusion seen with arterial stroke. Moreover, alternative outflow channels may allow some perfusion to occur, albeit at lower rates. It has been suggested that the presence and efficiency of venous collaterals, as well as recanalization, may have an impact on brain tissue damage and hence on the prognosis of acute CVT [17].

In arterial stroke, the change in diffusion is thought to be due to failure of cell water homeostasis caused by disruption of the energy-dependent membrane pump that prevents intracellular accumulation of water against an osmotic gradient. However, there is no direct relationship between the onset of irreversible biomolecular events signaling cell death and restriction of intracellular water diffusion. Cell swelling begins as the effectiveness of the membrane pump diminishes with decreasing delivery of energy substrates. If blood flow is restored before irreversible events occur, it is conceivable that diffusion abnormalities could also reverse.

It has been speculated that diffusion changes in venous infarcts may be initially due to an increase in transcapillary and interstitial pressure, causing restriction of diffusion, rather than ischemia leading to failure of the ion pump [15, 16]. There may be little or no energy failure, at least initially, contributing to a wider time window in which diffusion changes are reversible.

Neuronal loss depends not only on the degree of blood flow reduction, but also on its duration. In penumbral tissues surrounding the core of infarction, irreversible events have not yet occurred because flow reduction is less profound. There is thus a “period of grace” wherein timely restoration of blood flow permits cell recovery—a concept that forms the basis of modern stroke management.

In venous thrombosis, the perfusion deficit is less profound. However, if it persists for long enough, cellular homeostasis can fail, leading to cytotoxic edema and cell death. Since the perfusion deficits are less catastrophic, it is conceivable that a large population of cells exists in which “intracellular edema” with restricted diffusion is present, but the biomolecular events leading to irreversible cell death have not yet occurred. We believe that the brain affected by venous occlusion behaves more like the penumbral tissue in arterial ischemia. Reopening of venous occlusion can then lead to restoration of cell homeostasis, reversal of ADC reduction, and prevention of cell death in much the same way as in the penumbral region in arterial stroke.

We speculate that the hemodynamics in CVT initially lead to “intracellular edema” which is reversible for an undefined, variable time. This would explain the complete disappearance of restricted diffusion seen in this case, despite extensive venous thrombosis and gross

neurological deterioration for several days before recovery. The dilated petrosal sinuses and superior ophthalmic vein probably provided an alternative venous outlet, allowing enough perfusion to maintain cell viability, despite the presence of restricted diffusion. We suggest “intracellular” rather than cytotoxic edema be used when referring to restricted diffusion in CVT, as the latter is generally claimed to imply irreversibility and cell death.

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