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Segmental cerebral vasoconstriction: successful treatment of secondary cerebral ischaemia with intravenous prostacyclin

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Abstract

We describe a 23-year old male patient who presented with spontaneous intermittent and increasing attacks of severe, left-sided thunderclap headache combined with rapidly progressive muscle weakness and dysphasia, including gradual loss of consciousness. Subsequent CT, MRI and DSA showed progressive brain ischaemia and oedema within the left cerebral hemisphere with strict ipsilateral segmental arterial vasoconstriction. Despite extensive medical care, including steroids, the patient deteriorated rapidly. However, the clinical course changed dramatically within 15 h after the start of an intravenous infusion of prostacyclin at a dose of 0.9 ng/kg/min, with an almost complete recovery of consciousness and speech. In addition the patho-physiological alterations seen on MRI and DSA (including DWI/ADC) shortly before prostacyclin treatment were clearly reduced when the patient was examined 3–4 days later and he continued to recover thereafter. Although not fully compatible, our case had several clinical characteristics and radiological findings reminiscent of those of the “segmental reversible vasoconstriction syndrome”, sometimes called the Call-Fleming syndrome.

Key words: prostacyclin, dysphasia, segmental reversible cerebral vasoconstriction, thunderclap headache, cerebral ischemia, Call-Fleming syndrome.

Introduction

This case report describes the treatment with prostacyclin of a 23-year-old male patient who presented with spontaneously developed attacks of rapidly progressive intermittent left-sided thunderclap headache. The symptoms developed almost a year after an accidental fall from the fourth floor resulting in a left-sided subdural haematoma and a fracture of the C5 vertebra. The subdural haematoma had been acutely evacuated without replacing the bone flap. Apart from paraplegia the patient had recovered within a few weeks after the trauma. There was no indication of alcohol abuse, drug problems, previous episodes of cerebral vasculitis and recurrent headaches or family history of migraine in this previously healthy man. Except from taking anti-depressant (Fluoxetin, 20 mg), he used no pharmacological drugs.

The diagnosis remained unclear, but the symptoms showed similarities with those attributed to the "segmental reversible cerebral vasoconstriction syndrome", also called Call-Fleming syndrome (CFS) (1-4). Our patient worsened dramatically with dysphasia and loss of consciousness Radiological examinations including Magnetic Resonance Imaging (MRI) showed severe segmental cerebral vasoconstriction and progressive ischaemia, indicating focal cerebral hypoperfusion. He was now given synthetic prostacyclin (epoprostenol sodium, Flolan®; GlaxoSmithKline) on the basis of its feature of improving a compromised microcirculation in the brain as well as in other organs of the body (5, 6). To our knowledge, prostacyclin infusion has not been used previously as a treatment of cerebral vasoconstrictor syndromes.

Methods and material

Digital Subtraction Angiography (DSA) and Magnetic Resonance Image (MRI) protocols

A Philips Integris 5000 bi-plane unit (Philips Medical Systems, Best, the Netherlands) was used for all DSA. Routine protocols for morphological and functional MRI were done using a Siemens Allegra 3 Tesla and a Philips Gyroscan 3T MR-unit. Diffusion-weighted imaging (DWI) including apparent diffusion coefficient maps (ADC) and MR-perfusion (MRP) were

performed using standard practice and techniques. MRP maps of relative regional cerebral blood volume (rCBV), relative regional cerebral blood flow (rCBF), mean transit time (MTT) were done with the Lund perfusion program (LUPE) (7), and colour-coded after normalisation to the relative rCBF and rCBV values of the cerebellum (8). The arterial input function (AIF) was determined from an artery on the unaffected side.

Clinical course

Approximately 10 months after the accident, the patient suddenly developed intermittent severe left-sided headache. After one week of daily recurrence of thunderclap headache at intervals, which were resistant to various types of analgesics (paracetamol, naproxen and tramadol), he was referred from his domestic hospital to the Neurological Department and later on to the neuro-intensive unit of our hospital. He had been treated with ciprofloxacin for 2 days because of a urinary infection.

On arrival at our hospital, the patient was normally oriented and adequate, but showed episodes of recurrent severe left-sided headache accompanied by intermittent slight dysphasia. A computed tomography (CT) and subsequent CT angiography (CTA) of the brain were both normal except from sinusitis. There were no signs of vasculitis, vascular dissection, cerebral aneurysm or dural sinus thrombosis. A urine culture was positive for *E. coli* and antibiotic was changed to trimetroprim + sulfametoxazol. No indication of systemic or CNS infection were found. To exclude a concealed epileptogenic origin of the dysphasia, the patient was given a bolus dose of fosfenytoin (750 mg) and daily treatment with **c**arbamazepin.

The attacks of headache and dysphasia became gradually more prominent and his right arm became weaker. A CT scan (2 days after the initial one) showed signs of brain swelling and oedema, and patchy areas of hypo-attenuation within the white and cortical matter in the left frontal and parietal lobes. The EEG showed a slower pattern on the left side. At this stage, it was unclear wheather the lesions were of inflammatory, infectious or ischemic origin.

Prednisolon therapy, 50 mg/day, was initiated as a potential adjuvant and was given for 5 days.

On day 7 after arrival at our hospital, a selective digital subtraction angiography (DSA) of the anterior and posterior cerebral vascularity was done. The arteries of the right cerebral and cerebellar hemisphere were normal. On the left side, there was segmental and acute narrowing of multiple branches of the proximal, distal anterior and middle cerebral arteries (ACA and MCA) (Fig. 1 a), and in the left posterior cerebral artery (PCA). MRI including DWI of the brain showed brain swelling and large areas of hyperintense lesions (partially hypointense on ADC maps) in the left frontal and parietal lobes corresponding to mainly cytotoxic oedema reflecting acute ischaemia and to a lesser extent vasogenic oedema (Fig. 2 a, b and c). A lumbar puncture (LP) showed normal cerebrospinal fluid (CSF)

On day 9 after admission the right arm was fully paralysed, the patient became almost completely dysphasic, followed by unconsciousness. Intravenous prostacyclin infusion was started in the afternoon at a dose of 0.9 ng/kg/min. The next morning, approximately 15 h after the start of the prostacyclin treatment, the patient was fully awake and well oriented. His speech was close to normal, only mild dysphasia remained, and he could now move his right arm slightly.

An MRI including DWI and MRP 3 days after the start of prostacyclin treatment revealed a reduction of the brain swelling. The hyperintense lesions, including both vasogenic and cytotoxic oedema, showed no progression. The DWI and ADC patterns were significantly reduced, indicating that the pre-existing brain ischaemia was partially reversible (Fig. 2 d, e and f to be compared with Fig. 2 a, b and c). MRP showed secondary hyperperfusion in the areas distal to the previously demonstrated segmental vascular stenoses on DSA (Fig. 2 g). In addition, the periodic recurrent headache was less severe at this stage. Prostacyclin was discontinued gradually for about 10 hours.

Follow-up DSA 4 days after the start of the prostacyclin treatment showed a significant reduction of the segmental stenoses with almost complete normalisation of the previously narrowed vessels within the left ACA, MCA and PCA branches (Fig. 1 b).

The craniotomy was then covered with a cranioplastic operation using the removed bone flap. The headache disappeared successively over the following weeks. An MRI done 1 month later showed smaller areas of permanent brain infarctions (Fig. 3 a and b). At a next visit 2 months after leaving hospital, the motor function of his right arm was not normalized, but had improved significantly and his speech and mental status were normal.

Blood analysis in terms of haemoglobin, creatinin, urea, anti-thrombin concentrations and liver tests (bilirubin, GT ALAT and ASAT) were normal throughout the entire hospital stay. CRP and leukocytes as markers for vasculitis were normal or slightly above normal (highest values 40 g/L and 11×10^9/L, respectively). The CSF analysis showed normal levels of cells (poly 0.4 $x10^6$/L, mono $4x10^6$/L), protein 0.5 g/L, glucose 3.3 g/L and no IgG production. The patient had a normal blood pressure (range 120/70–95/60 mm Hg) throughout the whole hospital stay and there was no epileptogenic activity on EEG.

Discussion

Prostacyclin is an endogenous substance controlled by cAMP and produced in the endothelial cells of the vascular wall. It is important for maintenance of an adequate microcirculation (5, 6, 9). It is a vasodilator with anti-aggregatory, anti-adhesive and anti-inflammatory effects, and may reduce vasospasm after subarachnoid haemorrhage (10). The balance between prostacyclin and the vasoconstrictor and pro-aggregatory substance thromboxane A2 is disturbed in favour of thromboxane A2 under patho-physiological conditions (11), but can be re-established by infusion of prostacyclin. Prostacyclin has been shown to improve perfusion in the penumbra zone of the traumatised human brain (6) and to reduce the contusion volume in the traumatized rat brain (12). Based on these considerations, prostacyclin was given to our patient with the purpose of improving the cerebral circulation. Both the clinical and radiological symptoms were significantly reduced after the start of prostacyclin treatment.

The comprehensive picture showed some similarities with the “segmental reversible cerebral vasoconstriction syndrome” known as Call-Fleming syndrome (CFS) (1-4). The sudden onset of episodes of severe thunderclap headache and later-developing segmental narrowing in patches of cerebral microvessels in our patient are compatible with that syndrome. However, the symptoms are often bilateral, which was not the case in this patient. CFS has been related to precipitating factors such as migraine, porphyria, pregnancy and the use of vasoactive drugs and drugs of abuse, but it may also appear spontaneously, as was the case in our patient (2,3, 13 -14). The pathophysiological mechanisms are still poorly understood. The course of CFS is often benign, but there have been reports of cases with focal cerebral ischaemia sometimes leading to stroke or cerebral haemorrhage, resulting in permanent sequelae and even death (1-4, 13, 14). Steroid treatment has not been shown to be effective (14), as was the case in our patient. There is no established standard treatment that can reverse the syndrome. One case report described beneficial effects of intravenous use of the calcium channel antagonist Nimodipine (14), a finding that was not, however, confirmed in a subsequent larger study (3). Another case report indicated beneficial effects of the phosphodiesterase inhibitor Milrinone given intra-arterially (15).

In our patient, prostacyclin was given at an infusion rate compatible with endogenous production and it is safe without any side effects (16). The well-known features of prostacyclin (5,6,10) are compatible with the improvement in cerebral circulation that was apparent in this patient (Fig. 1 a, b), but we cannot exclude the possibility that the improvement occurred independently of prostacyclin treatment. However, this is less likely because, firstly, the progressive scenario of severe deterioration stopped almost immediately and, secondly, the improvement regarding consciousness, dysphasia and arm weakness appeared very soon after the start of the prostacyclin infusion. It is unlikely that normalisation of consciousness and speech within 15 h after the start of prostacyclin from a phase of deterioration can be explained by a spontaneous healing process only. In addition, there was a dramatic and rapid reversibility towards normalization of the radiological alterations noted on

DSA and MRI shortly after the start of the prostacyclin infusion (Fig. 2 d-f), and improved perfusion on MRP (Fig. 2 g), indicating that the ischaemia was partially reversible.

The craniotomy may have been a precipitating factor, as the headache and the vascular alterations occurred on the left side of the brain. On the other hand, there were no signs of headache during the first 10 months after the craniotomy, and the headache did not disappear immediately after the craniotomy was restored.

Cerebral vasculitis is an improbable differential diagnosis due to the normal CSF analysis (2,17), the acute onset of the apoplectic headache at intervals, focal neurological symptoms absence of vasculitis markers, and no fever. Further, there was an aggravation of symptoms despite the start of steroid treatment.

The signs of ischaemia on the MR images, the reduced consciousness, the right-sided paresis and the dysphasia (the patient was right-handed) can most likely be related to the cerebral vascular alterations seen in the left hemisphere – especially as the patient was improved regarding the dysphasia and consciousness relative to improvement of the cerebral circulation.

In summary: The present case report describes the use of prostacyclin infusion therapy in a young patient who spontaneously developed recurrent thunderclap headache, followed by fluctuating and progressive neurological deterioration combined with unilateral segmental vasoconstriction and secondary cerebral ischaemia. It seems reasonable to believe that prostacyclin had a favourable effect on the clinical and radiological course.

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Legends

Fig. 1. a. Left common carotid angiogram, lateral projection, showing segmented and acute narrowing of multiple branches of the proximal and distal anterior and middle cerebral arteries (ACA and MCA) (see arrows) 4 days before prostacyclin. **b.** Corresponding image 3 days after the start of prostacyclin infusion, illustrating a dramatic reduction and a partial normalisation of the previously narrowed vessels within the ACA and MCA territories (see arrows).

Fig. 2. An MR scan (axial T2W) 2 days before prostacyclin **(a)** and corresponding DWI (b-1200) image **(b)** showing brain swelling and large areas of hyperintense lesions in the left parietal lobe, and hypointensity on ADC **(c)** corresponding to acute cytotoxic oedema, i.e. ischemia. Corresponding axial T2W **(d)** and DWI/ADC **(e, f)** 3 days after the start of prostacyclin treatment reveal a reduction in the hyperintense lesions and in brain oedema. An MRP; a cerebral blood flow (rCBF) measurement 3 days after start of prostacyclin illustrates the increased perfusion in the previously ischemic region due to secondary hyperperfusion **(g)**. No new ischemic lesions were found. The corresponding MRP image before prostacyclin treatment is lacking.

Fig. 3. Follow-up MR done almost 4 weeks after ictus. Axial T2W **(a)** and DWI **(b)** images show minimal areas of permanent brain infarction and no acute ischaemia. The craniotomy has been covered by a bone implant, with an underlying and small postoperative subdural haematoma.

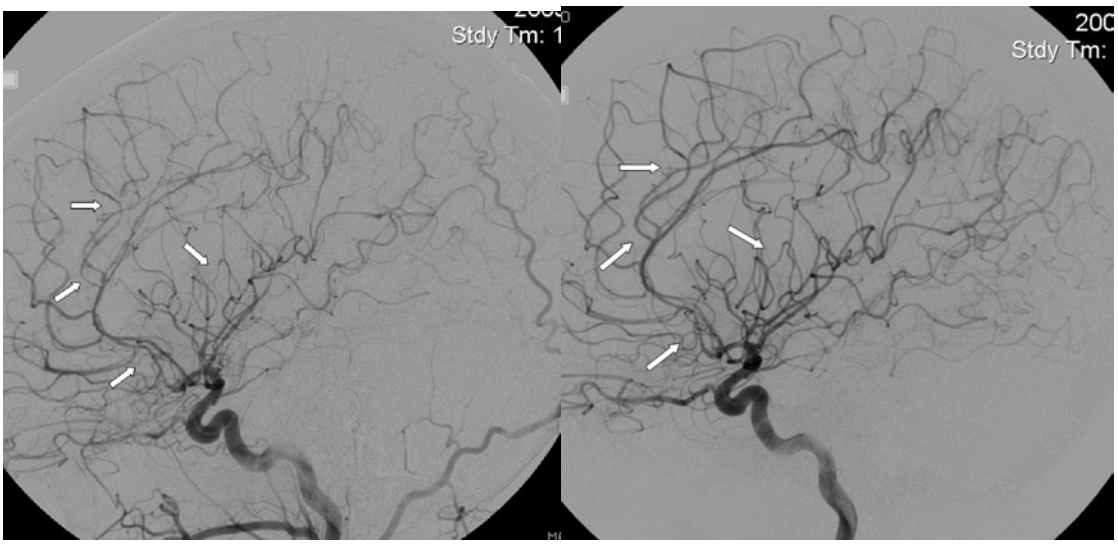
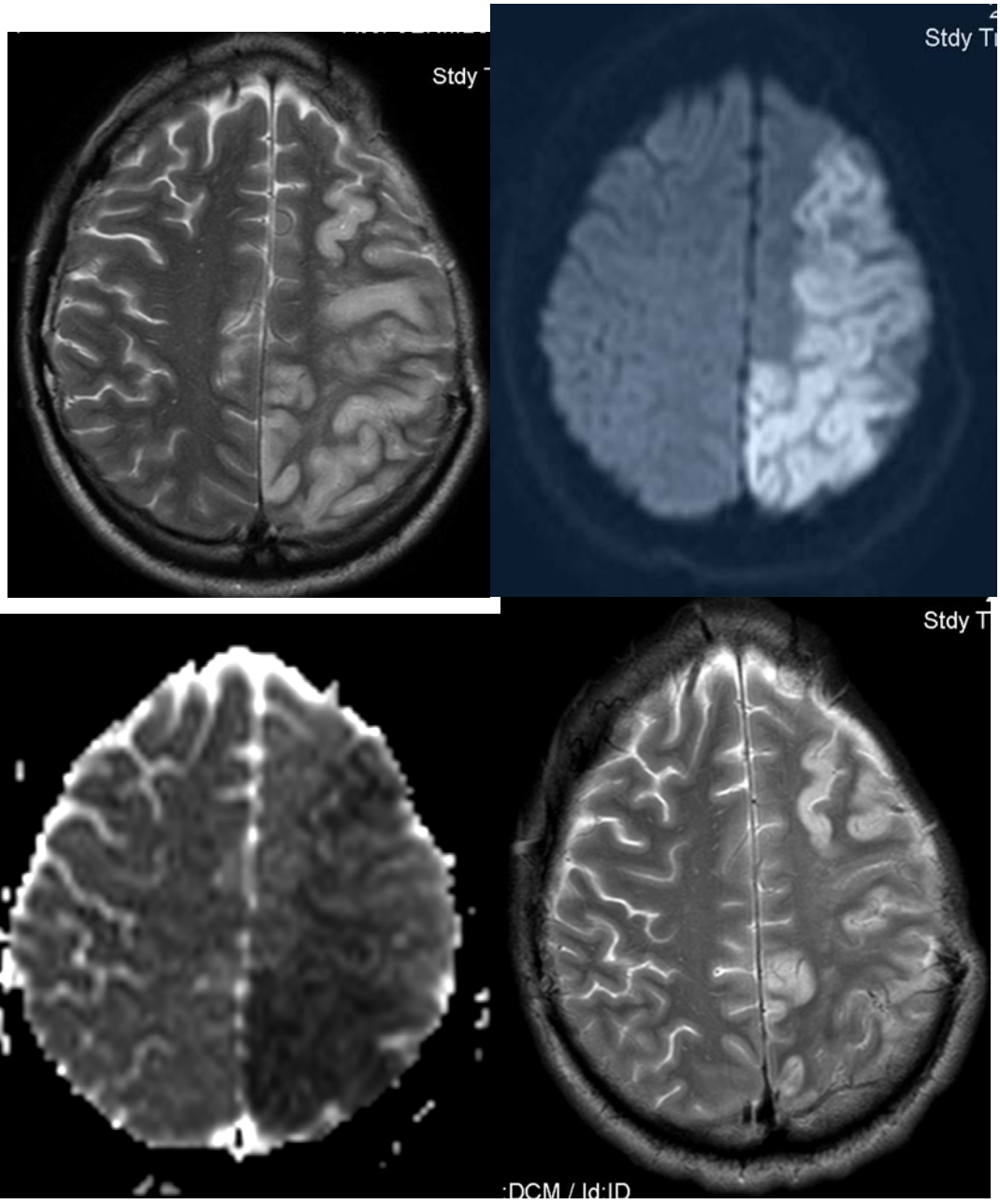


Fig 1a,b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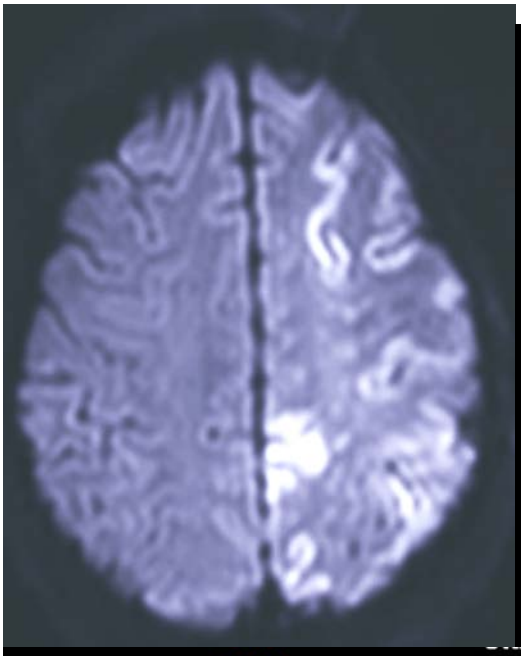

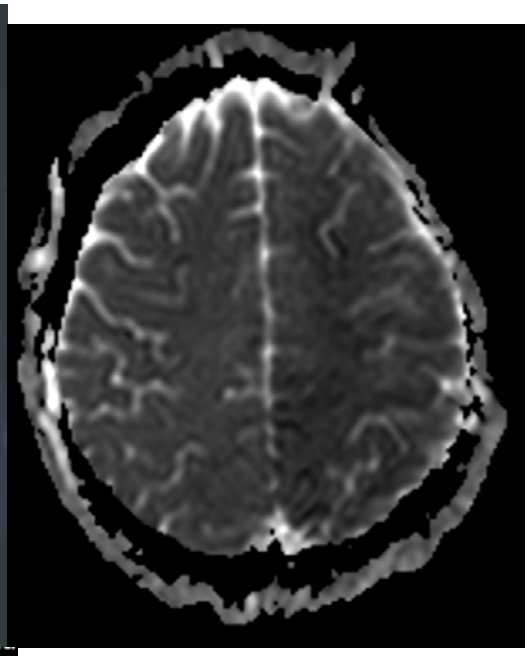

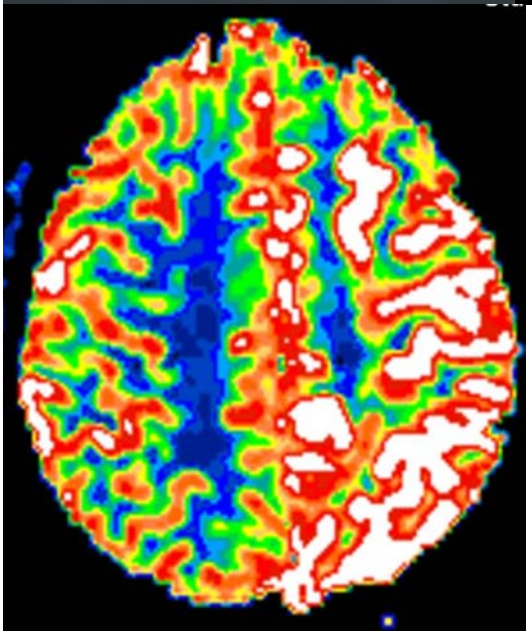

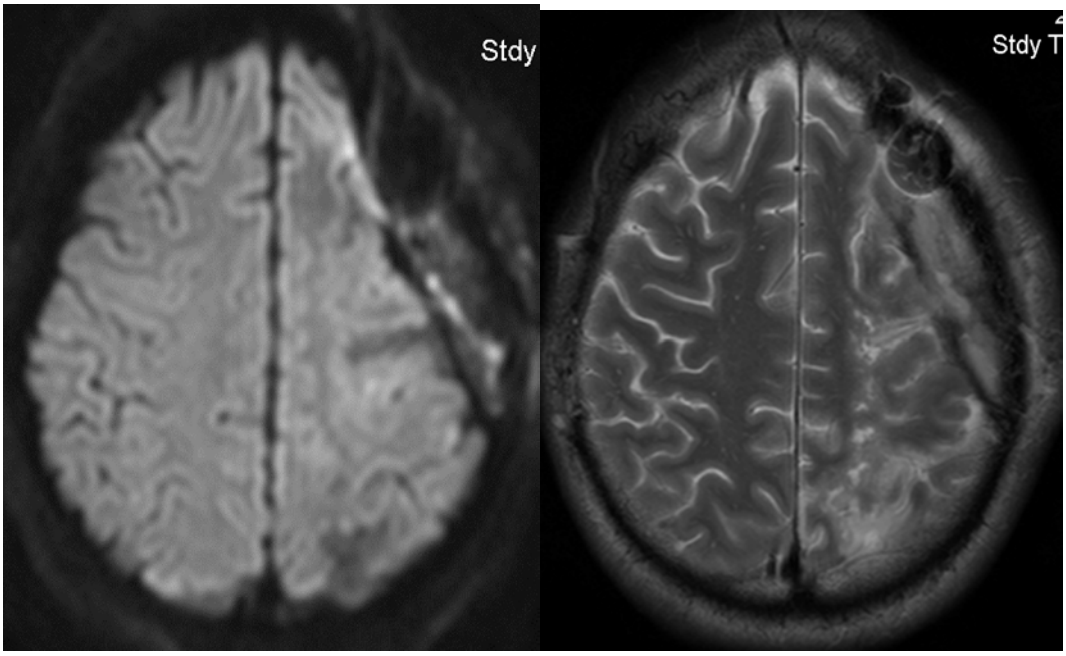

Figurerna kommer i ordning Fig 1a och b på en sida, Fig 2a-d på nästa sida, Fig 2 e-g nästa sida samt Fig 3a-b sista sidan