Infliximab-related seizures: a first case study

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ABSTRACT – Seizures following infliximab treatment are very rare and, to date, there is no detailed description of EEG abnormalities with cerebral radiological findings reported in cases with infliximab-related seizures. We describe a patient who acutely developed seizures temporally related to infliximab treatment, which disappeared after drug withdrawal. MRI showed encephalopathy involving mainly cortical regions and EEGs showed focal paroxysmal activity which completely disappeared a few days after infliximab withdrawal. No other plausible cause of the seizures was identified. The clear temporal association between seizure onset and infliximab treatment as well as the clinical improvement and disappearance of focal epileptiform activity after drug withdrawal indicated an evident correlation between seizures and infliximab therapy. The coexistence of pathological findings on MRI suggested that seizures were secondary to the encephalopathy. Further studies are required to evaluate whether infliximab per se has an epileptogenic effect or whether the seizures are caused by encephalopathy involving cortico-subcortical regions.

Key words: EEG, grey matter encephalopathy, infliximab, posterior reversible encephalopathy syndrome, seizures, TNF-α antagonists

Infliximab is a chimeric anti-tumour necrosis factor (TNF) monoclonal antibody with anti-inflammatory effects and is currently used for several inflammatory conditions such as plaque psoriasis, chronic inflammatory arthritis and severe active Crohn disease. Since its approval, several concerns regarding safety have been raised. The most commonly observed side effects are infections and hypersensitivity reactions, with only a small risk of developing lymphoproliferative diseases (Khanna et al., 2004). Rare cases of neurological complications have been reported and include Guillain-Barré syndrome/chronic inflammatory demyelinating polyradiculoneuropathy and neuropathy. Reports of seizures following infliximab therapy are scarce. The FDA Advisory Committee Review in August 2001 summarized cases of seizures associated with TNF-α antagonists (ACR, 2001); 29 cases
were reported with an estimated 170,000 patients exposed to infliximab worldwide and 26,104,000 exposed to etanercept worldwide. In recent post-marketing reports, sporadic seizures have been reported in patients receiving TNF-α antagonists. However, data on seizures are sparse, anecdotal and without valid comparison or control (Khanna et al., 2004). A pre-existing seizure disorder at present does not seem to be a contraindication to TNF-α therapy. Similarly, no cases of seizures following treatment with the new anti-TNF drug adalimumab, in post-marketing safety reports and analyses of global clinical trials, have been reported (Schiff et al., 2006).

We describe a patient who developed seizures after infliximab treatment for Crohn disease. MRI showed encephalopathy involving mainly cortical regions and EEG recordings showed focal paroxysmal activity which completely disappeared a few days after infliximab withdrawal. To our knowledge, there are no previously reported cases of infliximab-induced seizures with detailed description of EEG abnormalities combined with cerebral radiological findings of encephalopathy involving mainly cortical regions.

Case study

A 74-year-old man was admitted to our hospital to receive a second administration of infliximab for Crohn disease. His medical history was notable for HCV cirrhosis with normal liver function and for an ischaemic right temporo-occipital stroke, which occurred 11 years before, associated with mild left upper limb monoparesis and lateral homonymous hemianopsia. Brain MRI performed one year before admission to our hospital showed previous ischaemic infarction with cavitation in the right parieto-occipital region. No history of previous seizures was reported by the patient.

He had been suffering from Crohn disease for 22 years and had received a first infliximab injection two weeks before admission to our hospital, without any side effect. He was also receiving prednisone (25 mg/day) and mesalazine (5-amino salicylic acid; 800 mg bid). Two days after the second infliximab administration (5 mg/weight), he suddenly developed behavioural changes characterized by clusters of short episodes with sudden impairment of consciousness, amnesia and arrest of volitional movements. The episodes lasted for more than one minute and were followed by confusion and disorientation, alternating with periods of normal behaviour. Aggressiveness was present only when physicians or nurses tried to control him immediately after these short episodes of impairment of consciousness. There were no limb or orofalimentary automatisms, posturing, rotation, or clonic movements, and no secondary generalised tonic-clonic seizures.

Laboratory data were normal, excepted for mild hyponatraemia (133 mmol/L). Ammonium and transaminase levels were normal.

Brain 1.5 T MRI, performed one week after the second infliximab administration, showed not only the previous ischaemic infarction with cavitation in the right parieto-occipital region, but also a cortico-subcortical zone of altered signal, most clearly evident on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images in pre-frontal and limbic gyrus of both sides (figure 1). Some similar findings were found in the left insular lobe and in bilateral temporo-polar regions. There were no abnormalities on diffusion-weight scans. After gadolinium administration, there was only a mild enhancement on T1-weighted images in bilateral lower medial frontal lobes.

These radiological findings were compatible with an encephalopathy involving cortico-subcortical regions. A second and third MRI scan, performed five days and one month later, respectively, showed the same cerebral findings.

Two days after the onset of behavioural changes, a first standard EEG recording was performed (figure 2), which showed a background activity in the alpha range with a relative amplitude reduction in the

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Figure 1. Cortico-subcortical zone of altered signal in pre-frontal and limbic gyrus of both sides and a previous ischaemic infarction with cavitation in the right parieto-occipital region (FLAIR).
right parieto-occipital region, but with subcontinuous sharp-wave discharges, sometimes of great amplitude, in the left frontal region without any tendency to diffuse to contralateral regions. No diffuse slowing was evident. During the recording, the patient was cooperative, without any behavioural abnormalities. He only explained that he had felt unwell the day before.

In order to evaluate whether the paroxysmal EEG activity was related to infliximab treatment, we decided not to initiate any antiepileptic treatment, but rather discontinue infliximab treatment. The following day, another EEG was performed, showing the same paroxysmal discharges. Two days later, a third EEG was recorded and, unexpectedly, no longer showed any paroxysmal activity. Two others EEGs were performed during the following weeks without evidence of focal abnormal epileptiform activity in the left frontal regions. Also, the clinical features of the seizures pointed to an involvement of frontal/temporal anterior regions.

In our patient, both symptoms and neuroradiological findings (cortico-subcortical T2-weighted and FLAIR hypertintensities, and no abnormalities on diffusion-weighted images) resembled those encountered in posterior reversible encephalopathy syndrome (PRES), an acute encephalopathy usually associated with headache, seizures and areas of increased T2 signal in the posterior quadrants of the brain on MRI. The anomalies involving mainly frontal and temporal cortical regions did not allow us to make a definitive diagnosis of PRES. However, we could not rule out PRES with any certainty, since this syndrome is not necessarily associated with posterior regions of the brain and can also affect grey matter (Hinchey et al., 1996; Stott et al., 2005). PRES is related to many conditions and is associated with methotrexate (Renard et al., 2004; Dicuonzo et al., 2009; Erbetta et al., 2008), cyclosporine and asparaginase (Erbetta et al., 2008) treatment. Recently PRES has been described following infliximab infusion in a 14-year-old boy affected

**Discussion**

In the case study presented here, we describe a patient, with no prior seizure history, who acutely developed seizures temporally related to infliximab treatment. The rapid and complete regression of symptoms together with MRI findings allowed us to rule out both an ischaemic event and an infective or metabolic encephalopathy (ammonium and transaminase levels were normal, thus hepatic encephalopathy was ruled out), but rather suggested neurotoxicity related to infliximab treatment as a cause of the seizures.

Epileptiform discharges were located in the left frontal regions; thus, it is unlikely that the previous right parieto-occipital ischaemic lesion was the primary epileptogenic zone. Also, the clinical features of the seizures pointed to an involvement of frontal/temporal anterior regions.
by Crohn disease (Zamvar et al., 2009). The patient described in that report complained of visual disturbance and probable occipital lobe seizures followed by generalised tonic-clonic seizures, five days after the first infliximab administration. Both clinical and MRI features were compatible with the diagnosis of PRES.

It has been suggested that the association between PRES and immunosuppressive drugs is a consequence of a direct exposure of the brain to these agents, secondary to damage of the blood-brain barrier (BBB) by direct toxic effects on the vascular endothelium, vasoconstriction and microthrombosis (Hinchey et al., 1996). In our case, we did not find radiological findings compatible with a diffuse perturbation of BBB, since we found only a local alteration of BBB in the bilateral lower medial frontal lobes. In our case, it seems therefore unlikely that an alteration of the BBB may explain the diffuse involvement of cortico-subcortical regions. Because of the high prevalence of seizures in PRES, some authors considered the seizures as a possible aetiolo- logical factor for neuroimaging findings (Minagar et al., 2001). According to this hypothesis, seizures would be a cause, rather than a consequence of PRES. Although we did not record any ictal discharges, interictal EEG recordings showed focal paroxysmal activity, unrelated to the previous cerebral ischaemic injury, which completely disappeared a few days after infliximab withdrawal. On investigation, no other plausible cause of the seizures was identified.

The mechanisms which underlie infliximab-related seizures are still unknown. Since our patient did not develop any side effect after the first infliximab injection, an idiosyncratic reaction to this drug seems unlikely, although it is possible that the encephalopathy detected on MRI was caused by the first, and not the second, infliximab injection. Because of the clear temporal association between seizure onset and infliximab treatment, and, similarly, the clinical improvement and disappearance of paroxysmal discharge after drug withdrawal, we suggest that there is a direct correlation between seizures and infliximab treatment. It is reasonable to hypothesize a direct effect of infliximab on seizures, given the clear correlation between clinical improvement (seven days) and infliximab elimination half-life (10 days). Moreover, based on the observations in our patient, it seems unlikely that infliximab per se could lower the epileptogenic threshold since, in this case, we had expected EEG abnormalities in the posterior right side, i.e. in the region of previous cerebral ischaemic injury. It therefore seems more likely that the seizures in our patient were a consequence of the encephalopathy which involved mainly cortical regions.

Further studies are required in order to evaluate whether infliximab per se has an epileptogenic effect or whether seizures are caused by an encephalopathy involving cortico-subcortical regions.

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

References


