Persistent BBB disruption may underlie alpha interferon-induced seizures

**Abstract** Generalized seizures during Interferon-alpha (IFN-α) therapy have been repeatedly described in about 1%–4% of patients. However, the mechanisms underlying IFN-α-induced seizures are not known. We describe a patient who developed partial and secondary generalized seizures during IFN-α therapy while displaying a focal disruption of her blood-brain barrier (BBB) corresponding with pathological electroencephalography (EEG). To test our hypothesis that IFN-α induces seizure activity, we exposed rat somatosensory cortices to clinically relevant concentrations of IFN-α in the acute *in-vitro* slice preparation or *in-vivo*. While acute exposure did not induce epileptic activity, recordings from slices exposed to IFN-α *in-vivo* one week prior to recordings revealed pronounced epileptiform activity in >80% of the slices. We propose that cortical exposure to IFN-α leads to the generation of an epileptic cortex, which explains the weeks of latency in patients from initial treatment to seizures, and stressing the importance of identifying possible BBB disruption among high-risk patients administered peripherally acting drugs.

**Key words** blood-brain barrier · interferon-alpha · seizure

**Introduction**

Interferon-alpha (IFN-α) is now used widely in the therapy of chronic viral hepatitis [8]. Side effects of therapy are usually mild and self-limited. However, severe side effects include involvement of the central nervous system including frank paranoia, confusion, coma and seizures [15, 16]. Seizures were originally described in association with high doses of IFN-α, however more recent reports documented grand mal seizures during therapy with low doses of IFN-α in approximately 1% of adult patients [11, 20] and 4% of pediatric patients [25].

An interesting characteristic of IFN-α-induced seizures is the duration of therapy (2–14 months) before their appearance with generalized slowing or abnormal foci in electroencephalography (EEG) [20]. The mechanisms underlying IFN-α-induced seizures are presently not known. We report a patient with IFN-α-induced seizures who displayed focal BBB disruption and EEG abnormalities. Animal experiments supported our hypothesis of the epileptogeneity of IFN-α under conditions of BBB disruption.

**Methods for animal experiments**

All experimental procedures were approved by the Berlin animal ethics committees and principles of laboratory care were followed.

**In-vivo animal preparation**

Adult male Wistar rats (180–250 g) were anesthetized with thiopental (40 mg/kg body weight) and placed into a stereotactic frame. The skin was disinfected and a sagittal incision was made. A 4 mm diameter...
The patient, a 40-year-old female, suffered from a headache and, after routine neuroimaging, was diagnosed with a small left parietal meningioma (Fig. 1A). A gross tumor resection was performed with no post-operative complications. Aside from persistent headaches, she displayed no further symptomatology or neurological deficit. During follow-up the patient was treated with carbamazepine (600 mg/day qid) as post-operative seizure prophylaxis as well as for her headache with only partial relief. Because of a continuous debilitating headache six months after surgery, an investigation was performed using brain computerized tomography (bCT), magnetic resonance imaging (bMRI), EEG and head computerized tomography (hCT) following the administration of $^{99m}$Tc-diethyl cysteinate dimer (Tc-ECD) for brain perfusion and $^{99m}$Tc-diethylenetriaminepenta-acetic acid (Tc-DTPA) for BBB integrity evaluation (with a one week inter-scan interval). bMRI and MRI revealed no intracranial pathology (Fig. 1A). EEG revealed a slowing over the left parietal region with no evidence of paroxysmal activity. SPECT revealed several small areas of decreased perfusion around the tumor bed with several regions of Tc-DTPA enhancement in the left parieto-temporal region, indicating focal BBB disruption (Fig. 1B). Retrospective quantitative analyzes of the patient’s digitized EEG (restricted to 23 electrodes with measured impedance of <10KΩ) revealed reduced power in the alpha range with slight increased power at the theta and beta ranges compared with control data. Low resolution electrotomography (LORETA) [13] confirmed the left parieto-temporal region, the respective region of focal BBB disruption, as the source for the abnormally high-power theta and beta activity (Fig. 1C).

Twelve months following surgery, while her condition (including headaches) remained stable, IFN-α treatment was initiated for chronic hepatitis. IFN treatment was discontinued and no further seizures occurred despite an unchanged antiepileptic drug regimen.