Clinical commentary

Epileptic Disord 2014; 16 (4): 546-53

Subclinical focal seizures as a sign of progression in gliomas

José L. Fernández-Torre [1,2,3], Miguel Hernández-Hernández [3,4], Juan Martino [5], Carmen Hinojo [6]

[1] Department of Clinical Neurophysiology, Marqués de Valdecilla University Hospital, Santander, Cantabria
[2] Department of Physiology and Pharmacology, University of Cantabria (UNICAN), Santander, Cantabria
[3] Biomedical Research Institute (IDIVAL), Santander
[4] Department of Intensive Medicine, Marqués de Valdecilla University Hospital, Santander, Cantabria
[5] Department of Neurosurgery, Marqués de Valdecilla University Hospital, Santander, Cantabria
[6] Department of Medical Oncology, Marqués de Valdecilla University Hospital, Santander, Cantabria, Spain

Received June 03, 2014; Accepted August 03, 2014

ABSTRACT – *Background*. Subclinical seizures are ictal electrographic discharges lacking signs of clinical seizures, behavioural alteration or subjective symptoms. The diagnosis and detection of this type of non-convulsive seizures remain challenging, and information is scarce regarding this electroclinical picture in subjects with gliomas. The aim of this report is to describe two patients with gliomas who, after treatment with surgery and radiotherapy, exhibited subclinical seizures on video-EEG monitoring, as a manifestation of recurrence or progression of their brain tumour.
Methods. Case report and video-EEG monitoring analysis.
Results. Two patients with gliomas were admitted to our neurosurgical unit after a generalized tonic-clonic seizure. Brain MRI revealed a recurrence of their tumour. The use of video-EEG monitoring allowed the detection and characterization of subclinical seizures in both patients that otherwise would have gone undetected. In both cases, subclinical seizures arose from the frontal lobe and were not associated with motor manifestations or subjective symptoms.
Conclusions. We emphasize that the existence of subclinical seizures in patients with gliomas is likely to be underestimated, and can occur in advanced progressive tumours. It is important to carry out continuous video-EEG monitoring in brain tumour patients who have had recent clinical seizures in order to be able to detect subclinical seizures and make appropriate diagnosis.

Key words: continuous video-EEG monitoring, electrographic seizures, gliomas, non-convulsive seizures, subclinical seizures, tumour progression

Correspondence:
José L. Fernández-Torre
Department of Clinical Neurophysiology, Marqués de Valdecilla University Hospital, Avda. Valdecilla, s/n. 39008 Santander, Cantabria, Spain
<jlfernandez@humv.es>
<ftorrenfc@hotmail.com>

doi:10.1684/epd.2014.0701

Epileptic seizures are a common feature in subjects with gliomas, and may complicate the management of these patients (Kerhof and Vecht, 2013). Tumour-related epilepsy may be associated with refractory seizures and has a significant impact on the disease evolution.

Seizure worsening or seizure recurrence may be associated with brain tumour progression and, therefore, may be a sign alerting the clinician to re-evaluate with neuroimaging. The identification of focal and/or focal secondary generalized tonic-clonic seizures (GTCSs) is apparent from a clinical viewpoint. However, the diagnosis and detection of non-convulsive seizures (NSzs) remain challenging, and information is scarce regarding this electroclinical picture in subjects with gliomas.

We report two patients with gliomas who had electrographic or subclinical seizures (SSzs), as manifestations of recurrence and progression of their brain tumour. We emphasize that the existence of this type of seizure in patients with gliomas is underestimated and stress the importance of obtaining continuous video-electroencephalogram (v-EEG) monitoring for brain tumour patients with a recent history of convulsive seizures in order to be able to detect SSzs and make appropriate diagnosis.

Cases reports

Patient 1

A 56-year-old man with an eight-year history of progressive left frontal low-grade oligodendroglioma, treated with surgery and radiotherapy, was admitted to our neurosurgical unit after a GTCS. He had experienced occasional complex partial seizures and/or GTCSs in the past, but antiepileptic treatment with phenytoin (PHT) had been stopped after three years of seizure freedom. Recent history revealed four episodes lasting several minutes over the prior month, consisting of the inability to speak and hypoesthesia on the right side of the face. Neurological examination was normal and Karnofsky Performance Status (KPS) was 90. Brain MRI revealed a recurrence of the tumour, involving the left superior frontal gyrus and supplementary motor area. The lesion volume was 25.4 cm^3. Treatment with phenytoin (300 mg/24h) was started. On day 2, a v-EEG study showed a discrete breach rhythm and focal irregular slow waves and spikes and sharp waves localized over the left frontal area (*figure 1A*). Hyperventilation induced three focal SSzs arising from the left frontal lobe (superior frontal [F3] and parasagittal [Fz] electrodes) consisting of rhythmic high-amplitude spikes and sharps waves (*figure 2*). The duration of the SSzs varied between 60 to 90 seconds. Seizures were not associated with motor signs nor was consciousness impaired, as evidenced by the correct answering of all questions posed by the EEG technician. Levetiracetam (1,200 mg/24h) was added, and over the ensuing days, two consecutive v-EEG studies (on day 5 and 9) captured a total of four SSzs, similar to those previously described. Oxcarbazepine (600 mg/24h) was added, and a final v-EEG on day 17 showed occasional slow waves over the superior frontal area, but no SSzs. Similarly, the patient described complete remission of the episodes mentioned prior to admission.

Patient 2

A 42-year-old man with a previous diagnosis of left frontal glioblastoma multiform treated with surgery and chemoradiotherapy with temozolomide was admitted to the emergency unit because of a GTCS. In the previous six months, brain MRI showed disease progression and he was treated with six cycles of bevacizumab. Two months before admission, tumour recurrence was detected and treatment with fotemustine initiated. The last cycle had been administrated five days before admission. He had no previous history of epileptic seizures, but was on prophylactic treatment with levetiracetam (1,200 mg/24 h). Head MRI disclosed progression of the lesion involving the left frontal lobe, corpus callosum, and right frontal horn. On neurological examination, he was conscious and oriented with mild right hemisparesis. An urgent v-EEG showed focal irregular slow waves with an occasional sharp appearance, localised over the left frontal electrodes (*figure 1B*). During this recording, we also captured two focal seizures arising from the left superior frontal region *(figure 3*). These seizures lasted from 60 to 70 seconds and were not associated with motor or subjective symptomatology. The doses of levetiracetam and corticosteroids were increased. Given the advanced state of the cancer, the family refused further aggressive intervention. On the following days, the patient remained asymptomatic and was discharged to the palliative care unit.

Discussion

Subclinical seizures are ictal electrographic discharges lacking signs of clinical seizures, behavioural alteration or subjective symptoms (Sperling and O'Connor, 1990; Zangaladze *et al*., 2008; Velkey *et al*., 2011). The use of v-EEG allowed the detection and characterization of SSzs in both patients that otherwise would have gone undetected. In both cases, SSzs arose from the frontal lobe and motor symptoms were absent. The frontal lobe plays a significant role in executive func-

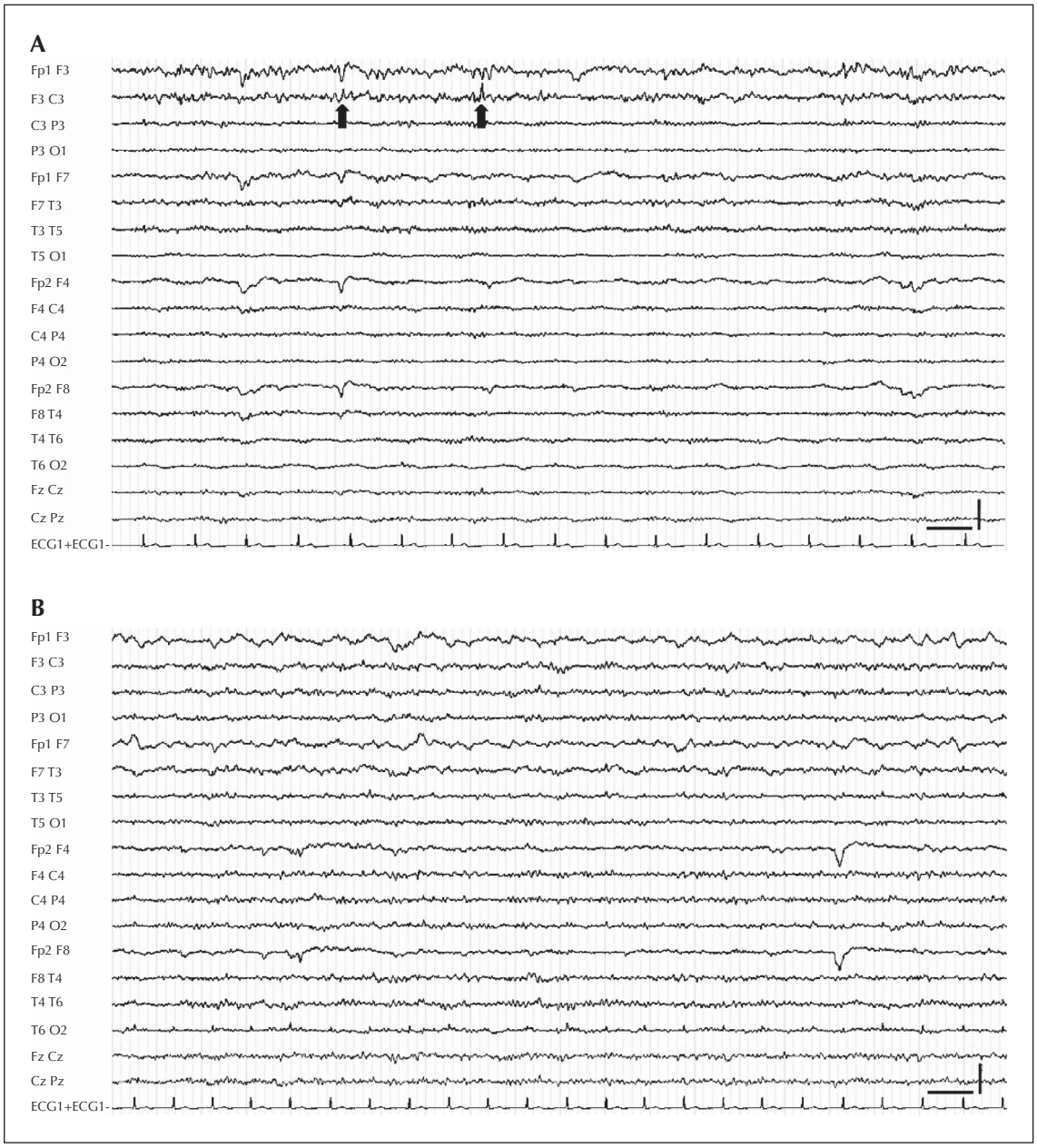

Figure 1. Interictal recordings.
(A) Note the presence of focal slow waves, spikes, and sharp waves (arrows), localized over the left frontal area.
(B) Focal slow activity with occasional sharp morphology, localized on the left frontal lobe.
Low filter: 0.5 Hz; high filter: 70 Hz; notch filter: 50 Hz. Vertical bar: 100 μV; horizontal bar: 1 second.

tions, working memory, and autobiographic memory, and since specific neuropsychological tests were not performed during the episodes, transient perturbation of these functions cannot be excluded. However, the unpredictable nature of the SSzs prevented greater verification. SSzs may recur and constitute a picture of non-convulsive status epilepticus (NCSE). Interestingly, in a recent study carried out among 1,101 brain tumour patients, the prevalence of NCSE, based on continuous v-EEG monitoring, was analyzed. Only 24% of patients had an EEG and 24 (2%) fulfilled criteria for NCSE (Marcuse *et al.*, 2014).

The important message is that detection of SSzs in patients with a history of a brain glioma may indicate progression or recurrence of the disease. Some reports have noted that secondary GTCSs and simple (focal motor) and complex partial seizures are the most common types of seizures in patients

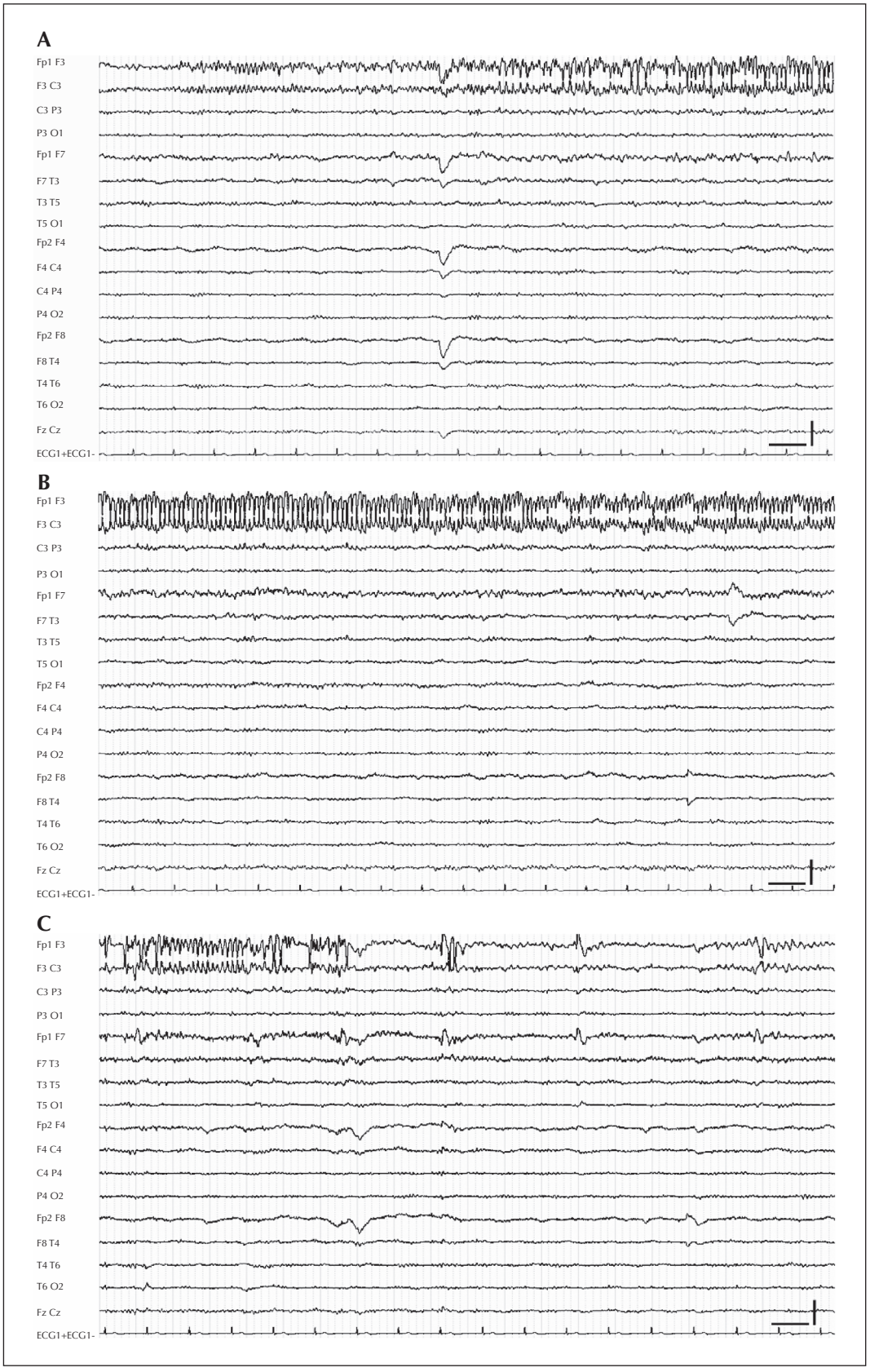

Figure 2. Ictal recording.

Figure 2. *(Continued)* (A) Onset of the seizure, with fast rhythmic low-voltage activity arising from the left superior frontal electrode (F3). (B) Progression of the seizure. Note that the fast activity evolved into high-amplitude rhythmic spikes. The seizure lasted 90 seconds and was not associated with motor manifestations or behavioural alteration. (C) End of the seizure.
Low filter: 0.5 Hz; high filter: 70 Hz; notch filter: 50 Hz. Vertical bar: 100 μV; horizontal bar: 1 second.

with gliomas (Englot *et al*., 2011; You *et al*., 2012). Surprisingly, we have not found studies in which the existence of SSzs in patients with brain tumours was investigated. Recently, Marcuse *et al*. (2014) found that a majority of seizures captured among patients with NCSE were electrographic, with 13 patients (54%) having only SSzs. In a quantitative and comprehensive literature review, seizure semiology predicted outcome. Simple partial seizures were one of the independent factors predicting poor seizure control (Englot *et al*., 2011). It is possible that the evolution to complex partial or GTCSs requires the recruitment of a critical volume of cerebral tissue and the existence of specific pathways, and therefore, focal restricted non-propagating seizures might be an indicator of advancing disease. Quite possibly, the location in the frontal lobe and the limited spatial extent of the lesion and seizure does not lead to an activation of a sufficient number of neurons to cause symptoms or observable signs (Zangaladze *et al*., 2008).

Not all subclinical seizures are related to brain tumours. The presence of SSzs have been described in association with many others clinical situations. Thus, SSzs are commonly observed during long-term v-EEG monitoring in patients who underwent presurgical evaluation. A few studies have addressed their clinical characteristics and prognostic value (Sperling & O'Connor, 1990; Zangaladze *et al*., 2008; Velkey *et al*., 2011). There are data suggesting that SSzs originate from the same cortical area as clinical seizures and generally indicate the localization of the epileptogenic zone (Zangaladze *et al*., 2008; Velkey *et al*., 2011). On the other hand, frequent bilateral temporal SSzs have been also reported in subjects after clinical remission in smoldering limbic encephalitis (Kanazawa *et al*., 2014). These patients had anti-voltage-gated potassium channel complex antibodies. It is also well-known that SSzs, NSzs, and episodes of NCSE occur frequently in sick hospitalized patients, particularly, in comatose individuals admitted to the intensive care unit (ICU) (Delanty, 2014). Interestingly, SSzs are frequently observed in the paediatric ICU population too, and it seems that they occur early after traumatic brain injury (Arndt *et al*., 2013). Yet, little is known about the neural consequences of these NSzs, and it seems that a high percentage may be undetectable on conventional scalp recordings. Whether aggressive treatment improves prognosis is something that still remains to be clarified.

In our cases, tumour progression was not just heralded by SSzs, as both patients had a GTCS at presentation after having been previously controlled. However, the detection of SSzs caused a change and optimization of antiepileptic treatment. The fact that patients with brain tumours are frequently referred for v-EEG monitoring following clinical seizures represents a referral bias (Marcuse *et al*., 2014). A reasonable approach for further research would be a prospective trial with continuous v-EEG monitoring in order to determine the incidence of SSzs in brain tumour patients and its prognostic significance.

The ictal EEG recordings shown here (*figures 2* and 3), from a neurophysiological viewpoint, were uncommon since focal spikes had similar morphology to those observed in intracranial recordings (Fernández-Torre *et al*., 1999). Indeed, epileptiform discharges during focal SSzs in our patients were shorter in duration and sharper than conventional spikes and sharp waves observed in routine scalp recordings. A technical explanation for this phenomenon might be the higher conductivity of the cerebral electrical signal resulting from the bone defect after cranial surgery. Therefore, in these patients, the antecedents of a previous neurosurgical intervention facilitated SSzs detection and recording. SSz are typically confined to a smaller area and appear to have lost the ability to propagate, which in brain tumours might be related to the destruction of the propagating pathways by increasing tumour growth. Moreover, in a patient with an intact skull, they may not activate a sufficiently large area of the brain (10-20 cm^2) to be visible (Tao *et al*., 2007). However, in tumour patients, the area with the highest risk of being epileptogenic is also the area typically exposed by a craniotomy, allowing detection of purely electrographic events.

There is universal consensus that prolonged convulsive seizures or convulsive status epilepticus frequently induce brain injury. In recent years, evidence has accumulated that in some cases, NSzs can cause neuronal damage (Fernández-Torre *et al*., 2006; Vespa *et al*., 2010). Therefore, the detection of SSzs may facilitate better management of antiepileptic drugs and possibly prevent further neuronal death by excitotoxicity. A recent special report by the International League Against Epilepsy (ILAE) recommends the use of long-term v-EEG for patients with a brain tumour, who are at risk of undetected and electrographic clinical seizures, or SSzs (Kennedy and Schuele, 2013).

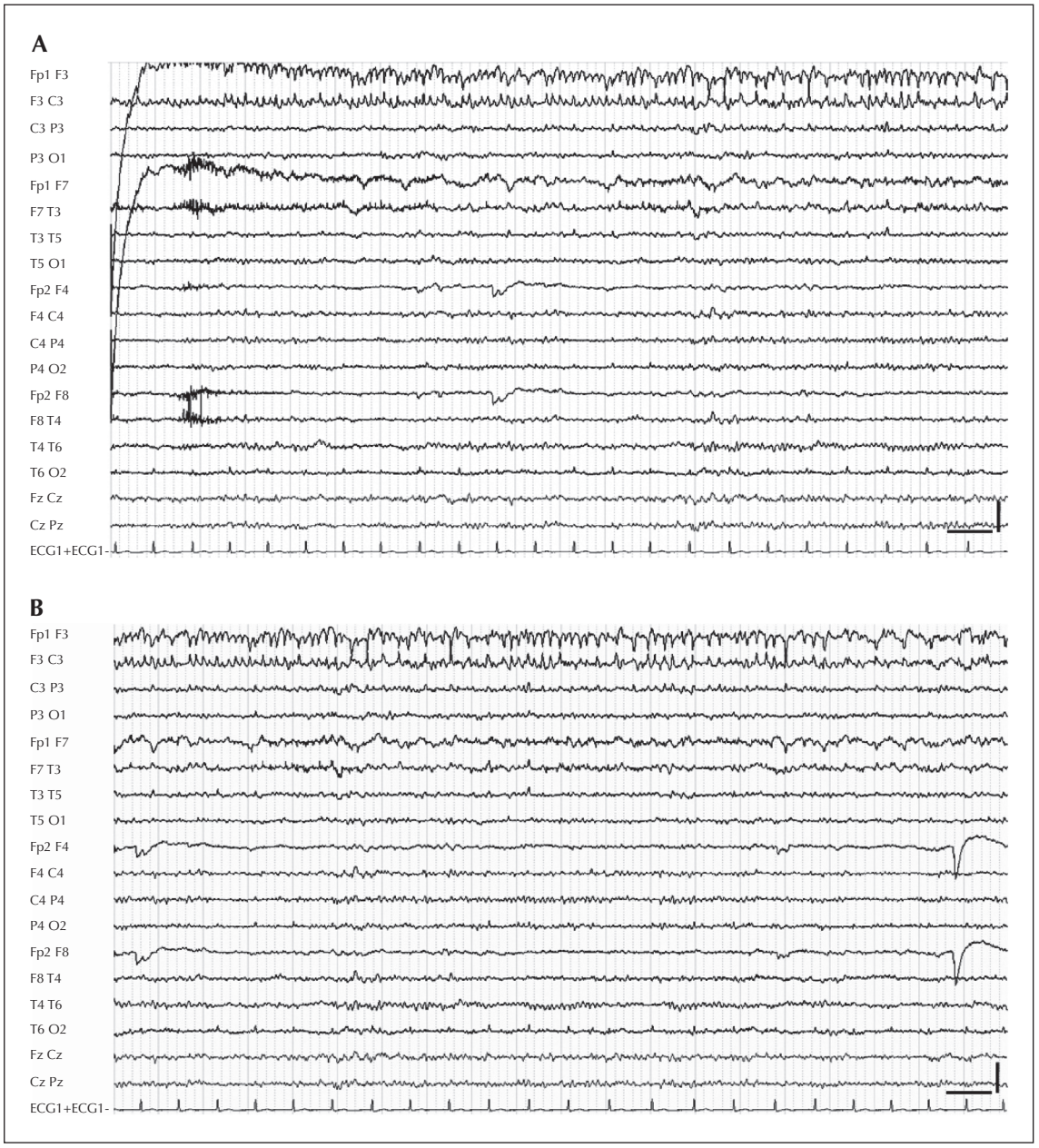

Figure 3. Ictal recording.
Note the occurrence of a subclinical left frontal seizure that lasted for 70 seconds in Patient 2.
(A) Onset of the seizure. (B) and (C) Fragments of the progression phase. (D) End of the seizure.
Low filter: 0.5 Hz; high filter: 70 Hz; notch filter: 50 Hz. Vertical bar: 100 μV; horizontal bar: 1 second.

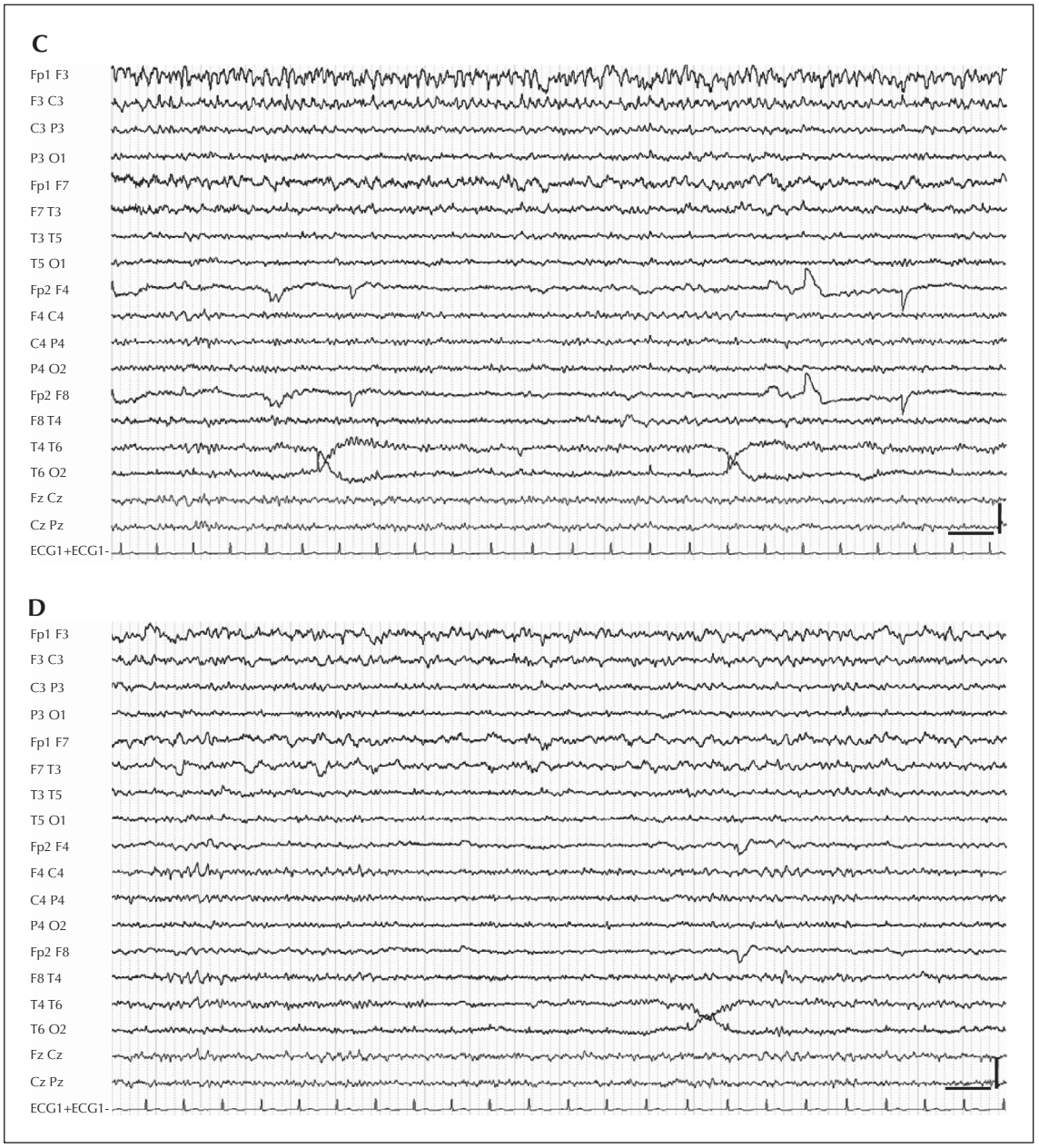

Figure 3. *(Continued)*

Conclusions

Subclinical seizures are likely underestimated in patients with gliomas and may occur in patients with progressive tumours. Continuous v-EEG monitoring is a helpful tool for detection and diagnosis, and our report and recent findings in the literature (Kennedy and Schuele, 2013; Marcuse *et al.*, 2014) provide some support for the use of this neurophysiological technique in selected patients with brain tumours and prior seizures. □

Disclosures

None of the authors have any conflict of interest to disclose.

References

Arndt DH, Lerner JT, Matsumoto JH, *et al*. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. *Epilepsia* 2013; 54: 1780-8.

Delanty N. Complex detection, complex decisions: more detail on subclinical seizures in the acutely sick brain. *Epilepsy Curr* 2014; 14: 129-30.

Englot DJ, Berger MS, Barbaro NM, Chang EF. Predictors of seizure freedom after resection of supratentorial low-grade gliomas. *J Neurosurg* 2011; 115: 240-4.

Fernández-Torre JL, Alarcón G, Binnie CD, *et al*. Generation of scalp discharges in temporal lobe epilepsy as suggested by intraoperative electrocorticographic recordings. *J Neurol Neurosurg Psychiatry* 1999; 67: 51-8.

Fernández-Torre JL, Figols J, Martínez-Martínez M, González-Rato J, Calleja J. Localisation-related nonconvulsive status epilepticus. Further evidence of permanent cerebral damage. *J Neurol* 2006; 253: 392-5.

Kanazawa K, Matsumoto R, Shimotake A, *et al*. Persistent frequent subclinical seizures and memory impairment after clinical remission in smoldering limbic encephalitis. *Epileptic Disord* 2014; 16: 312-7. doi: 10.1684/epd.2014.0664.

Kennedy J, Schuele SU. Long-term monitoring of brain tumors: when is it necessary? *Epilepsia* 2013; 54: 50-5.

Kerhof M, Vecht CJ. Seizure characteristics and prognostic factors of gliomas. *Epilepsia* 2013; 54: 12-7.

Marcuse LV, Lancman G, Demopoulos A, Fields M. Non-convulsive status epilepticus in patients with brain tumors. *Seizure* 2014; 23: 542-7.

Sperling MR, O'Connor MJ. Auras and subclinical seizures: characteristics and prognostic significance. *Ann Neurol* 1990; 28: 320-8.

Tao JX, Baldwin M, Hawes-Ebersole S, Ebersole JS. Cortical substrates of scalp EEG epileptiform discharges. *J Clin Neurophysiol* 2007; 24: 96-100.

You G, Sha ZY, Yan W, *et al*. Seizure characteristics and outcomes in 508 chines adult patients undergoing primary resection of low-grade gliomas: a clinicopathological study. *Neuro-Oncology* 2012; 14: 230-41.

Velkey Á, Siegler Z, Janszky J, Duray B, Fogarasi A. Clinical value of subclinical seizures in children with focal epilepsy. *Epilepsy Res* 2011; 95: 82-5.

Vespa PM, McArthur DL, Xu Y, *et al*. Non-convulsive seizures after traumatic brain injury are associated with hippocampal atrophy. *Neurology* 2010; 75: 792-8.

Zangaladze A, Maromi N, Liporace JD, Sperling MR. Characteristics and clinical significance of subclinical seizures. *Epilepsia* 2008; 49: 2016-21.

TEST YOURSELF

(1) How is a subclinical seizure defined?

(2) Mention a clinical situation in which subclinical seizures are frequent.

(3) What may suggest the existence of subclinical seizures in a patient with a brain tumour?

Note: Reading the manuscript provides an answer to all questions. You can check for the correct answer by visiting the Educational Centre section of www.epilepticdisorders.com