Clinical Neurophysiology Practice 10 (2025) 52–55

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

journal homepage: www.elsevier.com/locate/cnp

Case report

Within five weeks: Rapidly grown glioblastoma discovered on repeat MRI after pathologic EEG

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ARTICLE INFO

Keywords:
Case report
Epilepsy
Glioblastoma
Seizure

ABSTRACT

Background: According to the recommendations of the International League against Epilepsy, a timely workup with a brain MRI is recommended after a first epileptic seizure. However, if the MRI is unrevealing, it is normally not repeated.
Case Presentation: We present a patient with an unprovoked epileptic seizure and only slight focal abnormalities in the EEG and a normal brain MRI. Only 35 days later, after a third seizure and now a focally pathological EEG, we repeated the brain MRI and discovered a large mass in the left temporal lobe, which was resected and histologically classified as glioblastoma multiforme.
Conclusion: This case of a very fast-growing tumor suggests that recurrent seizures, with or without anti-seizure medications, or new changes in the EEG should prompt the clinician to consider a repeat brain MRI, even if the first scan was normal.

1. Background

The diagnosis of a brain tumor is typically made after inaugural symptoms, often seizures, and pathognomic brain imaging. In the event of normal brain imaging and an unremarkable clinical presentation, the median time to diagnosis can be prolonged (Chittiboina et al., 2012), presenting a clinical diagnostic challenge.

The prevalence of seizures in brain tumor patients varies substantially between studies even with similar histopathological types. On average, around 60 % of patients develop epileptic seizures (Audrey et al., 2022). Brain tumors account for approximatively 5 % of the cause of first-time seizures. Around 10 % of all focal seizures are caused by brain tumors (Banerjee et al., 2009, Carpio et al., 2024). Following the recommendations of the International League Against Epilepsy (ILAE), an MRI is advised after a first epileptic seizure. It should be conducted promptly to aid with diagnosis and to guide subsequent management (Fisher et al., 2014, Bernasconi et al., 2019).

We present the case of a patient with an unprovoked epileptic seizure and minor focal abnormalities in the EEG, with normal appearances on brain MRI. Only 5 weeks later, the patient was re-evaluated after a new seizure and significant focal EEG abnormalities suggestive of epileptic activity were detected. Therefore, we repeated the brain MRI, which revealed now a large mass in the left temporal lobe that classified histologically as glioblastoma multiforme (GBM) after resection, only 35 days after the first normal MRI scan.

2. Case presentation

A 53-year-old man was brought to our emergency department (ED) after a first bilateral tonic-clonic seizure when stepping off his bike after the ride home from work. In the days leading up to the seizure, he had experienced intermittent word-finding difficulties, but no seizure-provoking factors could be identified. His past medical history was free of previous epileptic events. Neurological examination revealed no deficits. Laboratory tests, aside from post-seizure elevated CK and lactate, were unremarkable. Lumbar puncture was not performed as there were no clinical symptoms suggestive of encephalitis. A head CT scan including angiography and perfusion was also unremarkable. After

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https://doi.org/10.1016/j.cnp.2025.02.002
Received 10 September 2024; Received in revised form 27 January 2025; Accepted 10 February 2025
Available online 22 February 2025

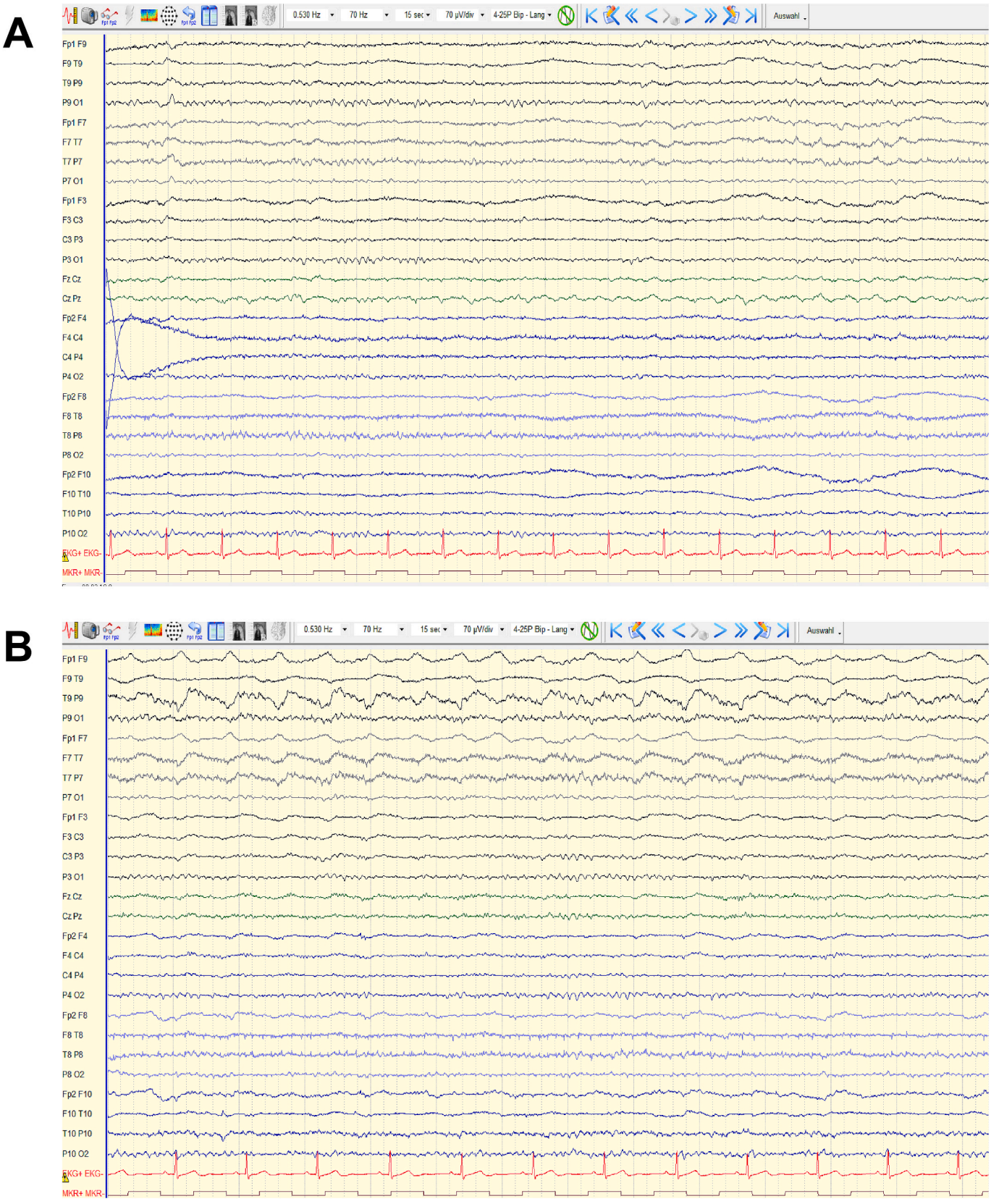

Fig. 1. EEG recordings from the patient. (A.) initial EEG the day of the inaugural seizure, showing intermittent focal theta-delta activity in the left frontotemporal region without clear epileptiform signs. (B.) Follow-up EEG after five weeks showing a continuous lateralized rhythmic delta activity (LRDA) in the left frontotemporal region suggestive of epileptic activity.

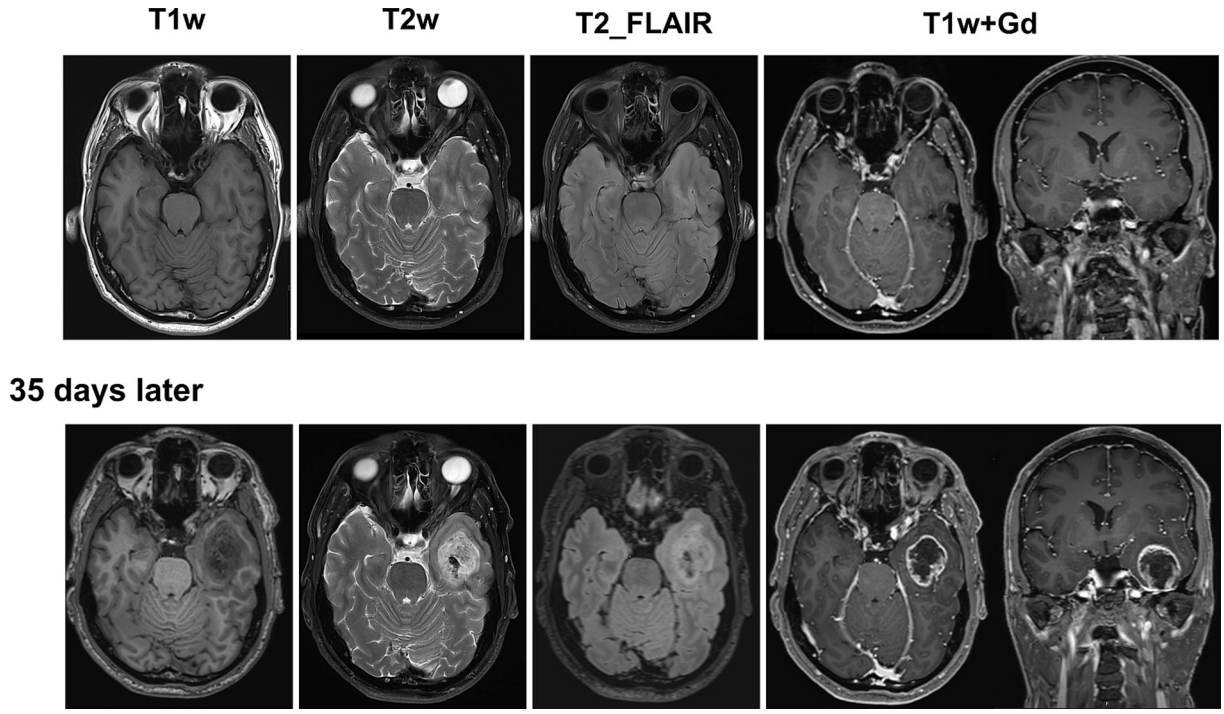

Fig. 2. Brain MRI in axial and coronal planes after the first inaugural seizure (top row), considered normal, and five weeks later (bottom row) across the region where the glioblastoma mulitforme appeared.

an initial recovery, the patient, experienced a second bilateral tonic-clonic seizure whilst still in the ED and was administered 1 mg of midazolam and 1 g of levetiracetam i.v.. An EEG on the same day showed some intermittent focal theta-delta activity in the left frontotemporal region without clear epileptiform signs, and signs of drowsiness (Ciganek's midline theta) (Fig. 1/A). Brain MRI revealed no structural or epileptogenic abnormalities and was reported as normal (Fig. 2/A). The diagnosis was of an unprovoked first focal to bilateral tonic-clonic seizure, and the patient was discharged in good general condition on levetiracetam 1 g/day p.o., and an EEG after sleep-deprivation was scheduled in the outpatient setting.

Five weeks after the initial event, the patient was readmitted to the ED following a further bilateral tonic-clonic seizure, and because of difficulty concentrating, a focal onset was presumed. The patient had reduced levetiracetam by himself to 500 mg/day because of poor tolerance with fatigue and depressive moods. Again, no other seizure-provoking factors could be identified. Additionally, the patient reported mild memory problems and word-finding difficulties during the recent weeks. No focal neurological deficits were observed, and lab tests were unremarkable. This time the EEG showed a continuous lateralized rhythmic delta activity (LRDA) in the left frontotemporal region suggestive of epileptic activity (Fig. 1B).

In view of this worsened EEG pattern, a second brain MRI was performed and now revealed a large contrast enhancing lesion in the left anterior temporal lobe (LWH 39 x 32 x 32 mm) (Fig. 2), with moderate mass effect and slight compression of the left lateral ventricle and mild midline shift, but without herniation. This lesion was suspicious for a primary brain tumor, and the patient was transferred to neurosurgery for resection of the lesion. Histologic analysis of the resected tumor confirmed a glioblastoma multiforme, IDH wild-type, WHO grade 4, with unmethylated MGMT status. Complete resection was achieved, and the patient is currently undergoing neurooncological treatment with combined radio-chemotherapy to 60 Gy combined with temozolomide (Stupp et al., 2005) followed by temozolomide with Tumor Treating Fields (TTF) (Stupp et al., 2017).

3. Discussion

Our case report describes a patient with two tonic-clonic seizures, subtle EEG changes, no prior neurological history and a normal MRI, which evolved into a significant GBM within only five weeks. GBM is known for fast growth rates, it has been described to double in size within around seven weeks. Such tumors can grow at a rate of 1.4 % volume per day, or an equivalent median volume-doubling time of 49.6 days. The average volume at diagnosis is around 17.7 ml (Stensjoen et al., 2015). In our case the rate of growth of the GBM was much faster than this previously reported, and therefore highly unusual. In our patient, the GBM developed a volume of 167.3 ml (volume = $4/3 \times \pi \times 39 \times 32 \times 32$ mm = 167.3 ml) within only 35 days after an initially unremarkable MRI finding.

A rapid growing GBM was described in the literature in two cases of pediatric patients, which appeared within just 1 week after a normal brain imaging (CT and MRI). These young patients experienced a survival of 6 years and 3 years-7 months, respectively, following tumor resection (Khalatbari et al., 2011). Another case report described two adult women, aged 60 and 51, whose only presenting symptom was headache, with a normal MRI following the initial work-up. In these cases, a diagnosis of GBM was made 3–4 months later, after repeating the MRI (Hakan et al., 2021).

Gliomas are the most common primary intracranial tumors and are associated with a number of changes that are involved in the pathogenesis of epilepsy, including edema and structural changes around the tumor, disruption of the blood–brain barrier, and molecular changes (Hills et al., 2022). The treatment of the tumor-associated epilepsy involves anti-seizure medication (ASM) as well as resection and radiochemotherapy of the tumor (van der Meer et al., 2022).

According to the ILAE-Guidelines, a diagnosis of epilepsy can be made after one unprovoked seizure. The probability of further seizures is similar to the general recurrence risk (≥60 %) (Fisher et al., 2014). Our patient suffered two focal to bilateral tonic-clonic inaugural seizures within 24 h, which were counted as one. In consideration of the pathological EEG findings with focal slowing, ASM was initiated, even

though the definition of epilepsy according to ILAE was not fulfilled. The patient reduced the initial dose of ASM himself, which might have led to a quicker manifestation of the second seizure. The decision to initiate a second short-term MRI control was mainly based on the extensive changes on the second EEG after the second seizure, in comparison to the previous EEG. The cognitive problems, with short-term memory and word finding difficulties, were only reported at the time of the second admission, and thus did not directly affect the decision to repeat the EEG. In our center, the first follow-up with EEG and clinical examination is usually planned three months after the first admission in an otherwise unremarkable case.

This case suggests that EEG and MRI should definitely be repeated as follow-up, also only a few weeks apart, if abnormal EEG findings were present, to clarify the relevance of the pathological EEG-pattern. Additionally, a clinical examination including neuropsychological screening, e.g. in the case of focal findings in the temporal lobe should be obtained. These considerations might lead to a significantly earlier diagnosis, and therefore a potentially better treatment of the still smaller GBM (Wood et al., 1988).

4. Conclusion

This case illustrates an unusual and remarkably rapid growth rate of glioblastoma multiforme, developing within 35 days after an apparently normal MRI. This case of recurrent seizures and pathological changes in the EEG, serves as a reminder to clinicians that a repeat EEG and depending on the result, also a repeat MRI scan should be considered—even if the previous scan was normal just a few weeks before.

Ethics approval and consent to participate

Written informed consent was obtained from the patient.

CRediT authorship contribution statement

Zsuzsanna Szankai: Writing – original draft, Writing – review & editing, Investigation. **Egle Huggenberger:** Writing – review & editing, Investigation, Methodology. **Christoph Metzler:** Visualization, Investigation, Formal analysis. **Christian Musahl:** Writing – review & editing, Methodology, Conceptualization. **Markus Gschwind:** Writing – review & editing, Methodology, Conceptualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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