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Clinical letter

Non-convulsive status epilepticus with negative phenomena—A SMART syndrome variant

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1. Introduction

SMART syndrome (stroke like migraine attacks after radiation) has been described as a late delayed side effect of cerebral irradiation and comprises prolonged, unilateral, neurological symptoms with transient, cortical gadolinium enhancement sometimes punctuated by seizures and ipsilateral EEG slowing [1]. Here we describe a patient with non-convulsive status epilepticus with prominent negative phenomena as an unusual manifestation of SMART syndrome.

2. Case

In 1995, at the age of 25 years, the patient was diagnosed with a right temporal brain tumour. The tumour was resected and histopathological analysis revealed a glioblastoma multiforme WHO IV, which was confirmed by a central reference, since the patient was treated within a clinical trial. Subsequently, he received focal brain irradiation (60 Gy) and adjuvant chemotherapy with ACNU and cytarabine. During follow-ups the patient presented without neurological deficits with a Karnofsky Index of 100%. Cerebral MRI showed post-therapeutic leukoencephalopathy but no signs of tumour recurrence. In November 2012, 17 years after the initial diagnosis, the patient was admitted to the hospital due to episodic headache and migrating numbness of the left arm, followed by ipsilateral flaccid sensorimotor hemiparesis lasting for several minutes. However, detailed history taken with the mother revealed a prior episode with impaired responsiveness and blank staring highly suggestive of a partial complex seizure. Cerebral MRI revealed no signs of tumour recurrence. CSF analysis was uneventful, whereas EEG showed marked delta slowing over the right hemisphere but no distinct spikes. Assuming right-hemispheric symptomatic epilepsy, levetiracetam was titrated up to 3000 mg/day. Twelve hours after discharge from hospital he presented again with headache and serial episodes of left sided marching numbness, sometimes accompanied by unresponsiveness. The neurological examination demonstrated left-sided persistent sensorimotor hemiparesis and neglect. Due to lack of neurological improvement and suspected ongoing seizures, continuous EEG monitoring for 3 days was performed, demonstrating marked right hemispheric, fronto-centro-temporal accentuated rhythmic 1.5–2 Hz delta slowing (Fig. 1). Over time, there were some dynamic EEG changes also demonstrating sharp waves over the right fronto-central and fronto-temporal regions (Fig. 1; online supplementary material). However, expansion of the antiepileptic treatment did not change EEG nor the clinical condition of the patient. Additionally, cerebral F-18 FDG-PET revealed marked increased cortical glucose metabolism of the entire right hemisphere and contralateral cerebellar diaschisis (Fig. 2A). Brain MRI now demonstrated slight diffusion restriction of the right pre- and post-central cortex (Fig. 2B). Tc-99 m HMPAO SPECT showed marked increased perfusion of the right hemisphere. Cerebral

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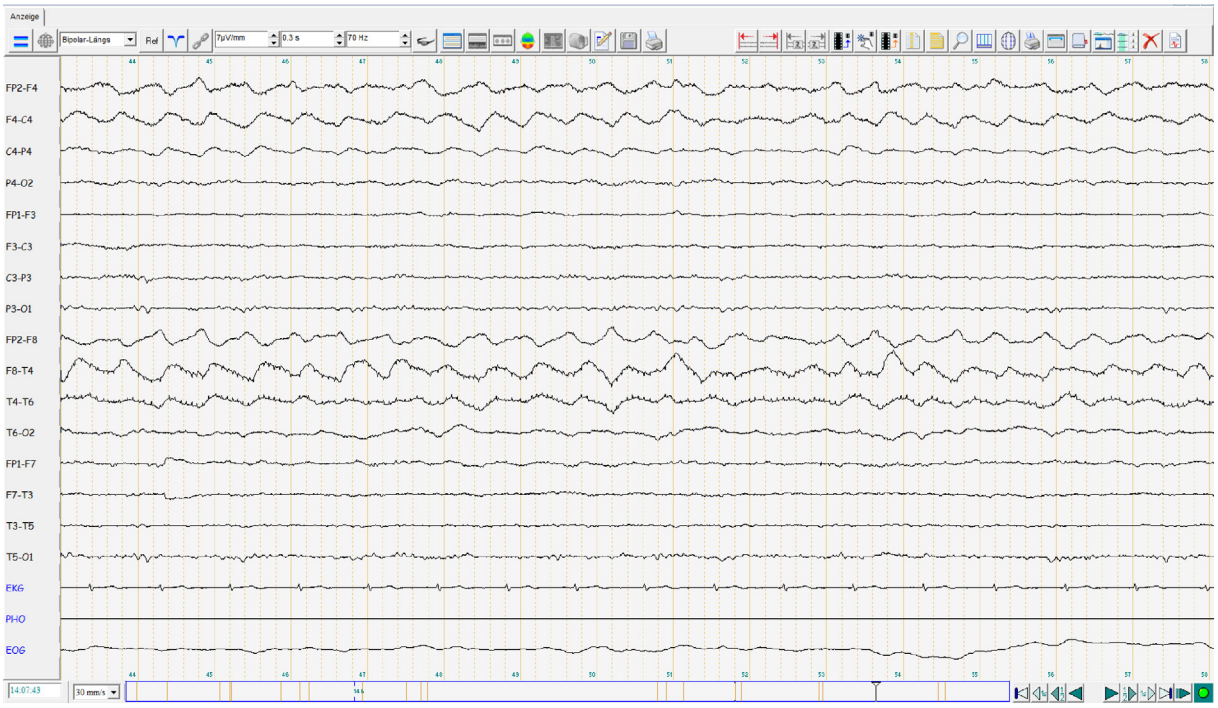

Fig. 1. Bipolar EEG Montage. Ictal EEG demonstrating rhythmic sharply configurated 1.5–2 Hz delta slowing over the right hemisphere, accentuated over the fronto-centro-temporal regions (4 days after symptom onset).

vasculitis and vasospasm were excluded by angiography. Again, extended CSF examinations showed neither signs of neoplastic meningitis nor infectious causes. Since we hypothesized a non-convulsive status epilepticus with persistent "negative" phenomena, a combined antiepileptic treatment was initiated [levetiracetam 3 g/day + lacosamide 400 mg/day ± phenytoine 750 mg ± topiratopiramate 200 mg/day, high-dose cortisone therapy] but no clinical and electrophysiological improvement was achieved. Consequently, the patient was referred to the neurological intensive care unit and anaesthetic therapy with midazolam (90 mg/h) and ketamine (200 mg/h) was administered for 72 h. After awakening from anaesthesia the patient exhibited marked clinical improvement with full recovery of motor function of his left leg, while motor function of the left arm continuously recovered to normal over a period of 2 months. Four days after anaesthetic therapy cerebral F-18 FDG-PET follow-up demonstrated right-hemispheric hypometabolism. At discharge, the patient was treated with levetiracetam 3 g/day, lacosamide 400 mg/day and perampanel 6 mg/day, respectively. One and a half years later, the patient remained seizure free, neurological examination revealed no deficits, EEG demonstrated sustained improvement (Fig. 2; online supplementary material) and brain MRI showed full regression of cortical diffusion restriction.

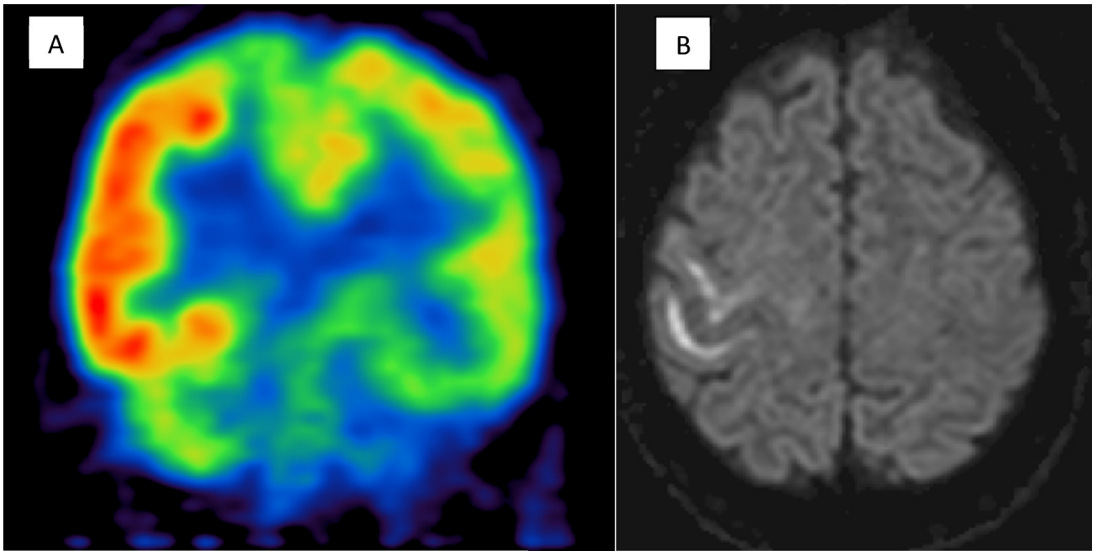

Fig. 2. (A) Cerebral F-18 FDG-PET with highly increased cortical glucose metabolism of the cortex of the right hemisphere with contralateral cerebellar diaschisis. (B) Cerebral MRI reveals diffusion restriction in the right pre- and post-central cortex 7 days after symptom onset.

3. Discussion

Seizures typically present with "positive" phenomena. However, ictal activity has also been described to be associated with negative symptoms [2,3] and it is even strongly recommended to consider seizures in the setting of unexplained deficits [3]. Similar to our patient, most such cases depicted in the literature, experienced a somatosensory sensation before or at the onset of the focal paresis in the same body region [2]. In our case, however, diagnosis still remained tricky though EEG, including continuous EEG monitoring, demonstrated rhythmic delta slowing but a lack of distinct continuous spike wave activity. This is not very unusual, if negative field potentials are confined to the deeper cortical laminae, as shown by Elger and Speckmann [4].

The results of MRI, cerebral F-18 FDG-PET and Tc-99m HMPAO SPECT strongly favour an ictal epileptic origin of the negative phenomena and vote against a postictal sign. Interestingly, the ictal state was refractory to several oral and intravenous antiepileptic treatments but ceased following anaesthesia with midazolam and ketamine. After a follow-up period of 16 months, including MRI, F-18 FET-PET and CSF studies, there were no signs of tumour recurrence. The patient remained seizure free, and all clinical and imaging abnormalities were completely reversible, except for the post-therapeutic leucoencephalopathy. Overall, the patient presented with characteristic clinical features of SMART syndrome, taking into consideration that the attacks commenced migraniforme headache and that the patient had a history of glioblastoma with multimodal therapy, including irradiation. However, our patient did not show gyriforme gadolinium enhancement as typically described in SMART syndrome [1]; in fact, the transient MRI changes more apply to changes seen as a result of prolonged epileptic seizure-activity. To our knowledge this is the first case report of non-convulsive status epilepticus with negative phenomena in a patient with a clinical presentation suggestive of SMART syndrome. The pathophysiology of SMART syndrome is not known. The clinical, electrophysiological and radiological characteristics from our case provide evidence that the prolonged neurological deficits and imaging abnormalities in SMART syndrome might result from epileptic activity.

Conflict of interest statement

None of the authors have any conflict of interest.

Authorship contributions

Eva Hametner contributed in study conceptualization and design, data acquisition, analysis and interpretation of data, drafting and revising the manuscript, giving final approval of the manuscript. Iris Unterberger helped in study conceptualization and design, data acquisition, analysis and interpretation of data, drafting and revising the manuscript, study supervision, giving final approval of the manuscript. Andreas Lutterotti helped in study conceptualization and design, critically revising the manuscript. Ronny Beer contributed in data acquisition, critically revising the manuscript. Manuela Prieschl contributed in data acquisition, critically revising the manuscript. Eveline Donnemiller contributed in interpretation of FDG and SPECT course, critically revising the manuscript. Astrid Grams contributed in interpretation of MRI course, critically revising the manuscript. Günther Stockhammer contributed in study conceptualization and design, data acquisition, analysis and interpretation of data, drafting and revising the manuscript, study supervision, giving final approval of the manuscript.

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