

Frequent sleep-related bitemporal focal seizures in transient epileptic amnesia syndrome: Evidence from ictal video-EEG

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SUMMARY

Two patients who shared similar presenting clinical features of anterograde and retrograde autobiographical amnesia typical of transient epileptic amnesia (TEA) underwent prolonged video electroencephalogram (VEEG) monitoring and were found to have sleep-activated epileptiform activity and frequent subclinical bitemporal seizures predominantly during sleep. Case 1 is a 59-year-old woman whose presenting complaint was memory impairment. Over 18 months, she had three distinct 8-h-long episodes of confusion and disorientation with persistent anterograde and retrograde autobiographical amnesia. VEEG recorded frequent interictal bitemporal sharp waves confined to sleep, and 14 subclinical seizures, also mostly during sleep. Case 2 is a 50-year-old woman with known focal epilepsy also presented with memory complaints. Over the course of 1 year, she had two discrete 2-h-long episodes of amnesia, with ongoing anterograde and retrograde autobiographical amnesia. VEEG recorded independent bitemporal sharp waves, and 14 subclinical seizures during sleep and drowsiness. Memory impairment improved in both patients with successful treatment of their seizures. Although the etiology of accelerated long-term forgetting (ALF) and remote memory impairment (RMI) in transient epileptic amnesia (TEA) is unknown, these cases suggest frequent sleep-related seizures may contribute, and they highlight the importance of video-EEG monitoring.

KEY WORDS: Transient epileptic amnesia, Sleep, Temporal lobe epilepsy, Ictal video-EEG.



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Transient epileptic amnesia (TEA) is characterized by anterograde and variable retrograde amnesia, a history of pure amnesic seizures with or without other seizure types, epileptiform abnormalities on electroencephalogram (EEG), and empiric response to antiepileptic drug therapy.¹ In many cases, amnesia is the patient's presenting complaint. Accelerated long-term forgetting (ALF) and remote memory impairment (RMI) are distinctive yet inconsistent interictal cognitive problems reported by most patients with TEA.² ALF is characterized by impaired recall of recently learned information after more than 24 h, despite normal immediate recall.³ RMI for autobiographical life events that took place many years prior to identified seizure onset is also characteristic in patients with TEA.³ The

pathophysiologic basis of these distinctive cognitive phenomena remains unclear, although recent functional neuroimaging studies have shown altered function of the right parahippocampal gyrus, right temporoparietal junction, and cerebellum and altered connectivity between the right parahippocampal gyrus and middle temporal gyrus,⁴ whereas pathology has suggested that bilateral hippocampal structural damage may underlie ALF and RMI in TEA, with findings of bilateral hippocampal gliosis.⁵ A recent study following long-term outcome found no elevated risk of dementia in their TEA cohort, though memory difficulties were often stably persistent.⁶

There have been few reports concerning the ictal characteristics of patients with TEA. We present ictal video-EEG data from two patients with TEA who demonstrated frequent focal temporal lobe onset subclinical or minimally clinical seizures arising from sleep, potentially explaining transient cognitive impairments typical of TEA.

CASE 1

A 59-year-old woman presented to the behavioral neurology clinic with a chief complaint of memory impairment. About 18 months prior to presentation, she had an 8-h event upon waking with confusion, disorientation, and cognitive slowing, although she remained interactive. She had two similar events over the next 4 months, for which she was amnesic. Brain MRI, carotid ultrasound, echocardiogram, and EEG were negative, and a provisional diagnosis of transient global amnesia had been made.

Following her first event, she began to experience memory impairment that significantly affected work, with inability to recall events within recent days, and variable retrograde amnesia for memorable personal events within several months but also extending to previous decades, including failure to recall a visit to another tertiary medical center earlier in the year, the death of her father (14 years prior), or her honeymoon (7 years prior). Neuropsychological evaluation showed only low-average learning and verbal retention, but was otherwise normal. Brain MRI was repeated and remained essentially normal. CT-PET of the brain showed mild generalized hypometabolism. Thyroid-stimulating hormone (TSH), serum and cerebrospinal fluid (CSF) paraneoplastic antibody panels, and CSF analysis were normal. Routine outpatient EEG recorded an electrographic seizure of unclear onset during sleep.

She was admitted to the epilepsy monitoring unit (EMU) for seizure quantification. Interictally, she had frequent independent bitemporal sharp waves during sleep, maximal on the left. Over 3 days of recording, she had 13 right and 1 left temporal lobe seizures lasting between 18 and 47 (mean = 35) seconds in duration (Fig. 1), including 11 from light non-rapid eye movement (NREM) sleep stages N1 or N2, and 2 from wakefulness. Awake-sleep state and duration information was unavailable for seizure 11.

Sleep-related seizures were unassociated with any symptoms except brief arousal. Initial treatment with levetiracetam was ineffective. A subsequent valproate trial fully resolved her seizures on prolonged EEG monitoring, with significant subjective improvement in cognition to a level near her baseline at 2 months' follow-up.

CASE 2

A 50-year-old woman with known focal epilepsy presented to the epilepsy clinic with memory complaints. She was first seen 6 years prior following a 2-h episode of amnesia with repetitive questioning but preserved orientation, leading to a provisional transient global amnesia diagnosis. One year later, she had a similar event upon waking in the morning, involving an additional inability to recognize family members. Sequential interictal EEGs showed independent bitemporal sharp waves, maximal left, predominantly during sleep. Brain MRI was negative. Levetiracetam titration to 1,250 mg twice daily was ineffective, with continued spells characterized by "glassy eyed" staring and impaired speech lasting up to 10 min every few months and cognitive problems, such as forgetting to perform assigned tasks at work and autobiographical RMI for events extending to 1984, including family weddings, vacations, and her honeymoon. She described that photos and videos of these events were like watching "somebody else's life." Neuropsychological evaluation showed impaired delayed auditory verbal memory and reading efficiency, but was otherwise normal. TSH, serum paraneoplastic antibody panel, and vitamin D levels were normal. She was admitted to the EMU for seizure quantification. Over 48 h, she had 14 temporal lobe seizures, 12 of right-sided and 2 of left-sided onset that lasted between 8 and 94 (mean = 44) seconds in duration, 11 during light NREM sleep, 2 during drowsy wakefulness, and 1 during sleep-wake transition. Clinically, there was only arousal from sleep and brief staring with confirmation of ictal amnesia by response testing and normal postictal language testing, but an inability to recall ictal testing. Oxcarbazepine 600 mg twice daily effectively resolved seizures by 48-h ambulatory EEG at follow-up 4 months later, with subjective improvement in memory and work performance.

DISCUSSION

Our two TEA patients shared the common typical clinical features of anterograde and retrograde autobiographical amnesia with evidence for focal epilepsy. Both had focal nonlesional bitemporal epilepsy, with a predominance of sleep-related focal bitemporal seizures and rarer daytime events, and sleep-activated interictal bitemporal epileptiform discharges. Both had distinctive episodes of amnesia on awakening, with subsequent confirmation by prolonged video-EEG of frequent sleep-related seizures that were not

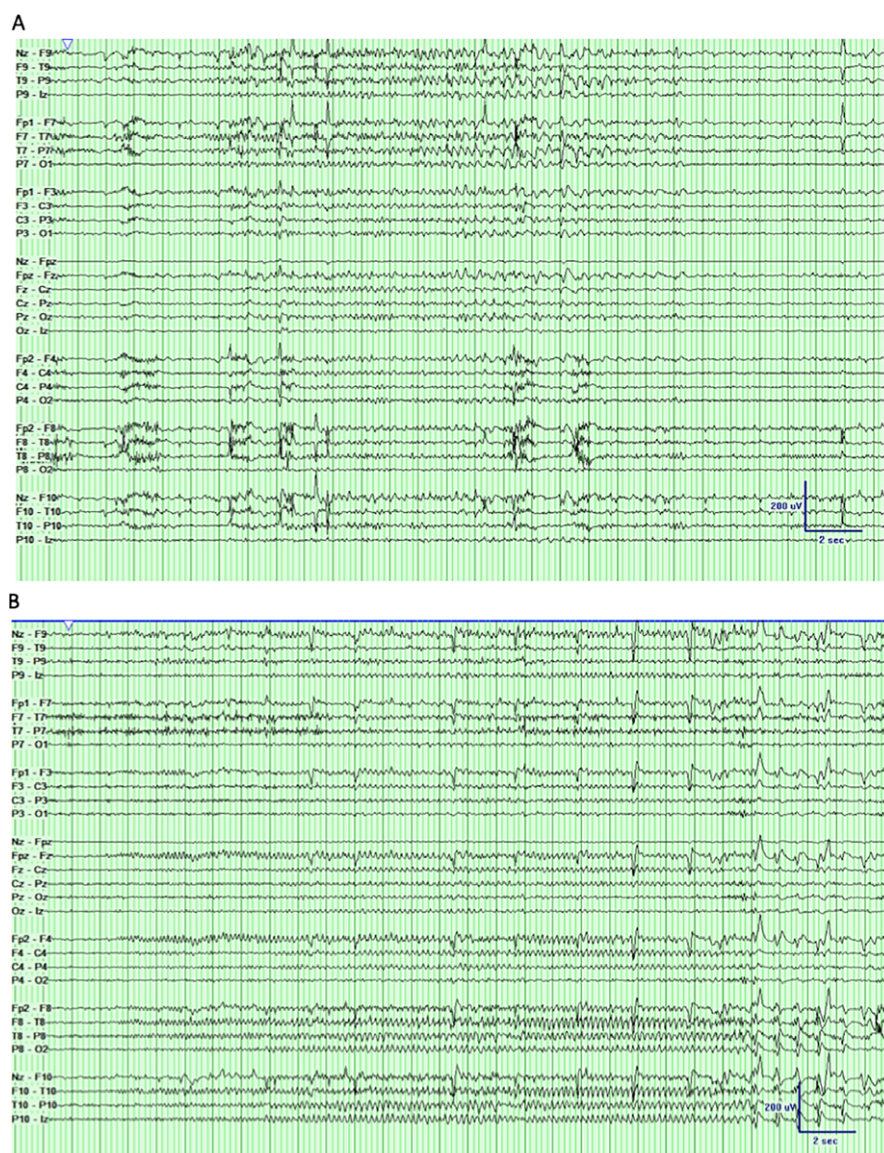


Figure 1. Example seizures from the (A) left and (B) right temporal lobes in case 1. *Epilepsia Open* © ILAE

previously evident to the patient, their families, or treating clinicians before ictal recordings. In our TEA cases, interictal cognitive symptomatology improved following treatment with antiepileptic drug therapy, suggesting that continuous EEG recordings should be considered early in the evaluation of patients with TEA who report continued cognitive dysfunction to exclude otherwise occult nocturnal seizures. Additionally, daytime focal impaired awareness seizures may be underrecognized and underreported unless specifically inquired about when obtaining the history. Elucidating this history, such as the “glassy eyed” spells in case 2, may prompt the care provider to further pursue subclinical seizures as a cause for the memory decline.

Previous case series have focused on interictal EEG manifestations.^{7,8} Reported ictal recordings in patients with TEA have been limited and have emphasized discrete waking amnesic periods, but have not described association with sleep or typical TEA symptoms of ALF and RMI.^{9–13} Both of our cases had frequent seizures with independent bitemporal onset primarily arising during sleep and subsequent resolution with institution of effective antiepileptic drug therapy. The seizures and response to therapy were documented with long-term continuous EEG monitoring and associated with subjective reports of memory improvement. To our knowledge, this is the first such report of these distinctive predominantly sleep-related, frequent

bitemporal onset ictal findings recorded during prolonged VEEG in patients with TEA.

Memory impairment, either in the form of ALF or RMI, is usually seen in patients with TEA, although it is not considered as requisite in the currently proposed TEA diagnostic criteria.¹ Both of our patients reported prominent memory issues, with striking RMI. The specific pathophysiology behind ALF and RMI is unknown, although frequent subclinical seizures or subtle structural pathologic changes have been advanced as plausible causes,³ and subtle bilateral mesial temporal atrophy has been reported in some TEA patients, although it has not been correlated with ALF or RMI.¹⁴ Clinically, there has been evidence for bitemporal epileptiform abnormalities in 14 out of 24 (58%) patients in one series of 30 TEA patients.⁸ Bitemporal epileptiform discharges were seen in 22 of 37 (56%) TEA patients who reported laterality in a review of all reported cases as of 2005.³ Aligning with these data, our two patients also showed prominent independent bitemporal interictal epileptiform discharges (IEDs) and seizures. It is possible that focal temporal epileptogenic pathophysiology plays an even more significant role than structural changes in mediating ALF and RMI in TEA.

Sleep activation of interictal epileptiform discharges is a prominent feature in TEA. Up to 74% of TEA patients have amnesic events upon morning awakening, with 30% having symptoms exclusively after awakening.⁷ One study of 30 patients with TEA demonstrated IEDs on awake EEG in 17 of 30 (57%) patients, but IEDs increased to 24 out of 25 (96%) patients with recorded sleep.⁸ In the largest studied TEA cohort, 44% of patients with recorded IEDs had them exclusively during sleep.⁷

Sleep is crucial for memory, suggesting that the prominent sleep-related epileptiform discharges and seizures seen in our TEA cases may play an important role in the distinctive ALF and RMI amnesia frequently endorsed by TEA patients. Sleep is thought to facilitate memory formation, and N3 and REM sleep stages are particularly important.¹⁵ Our patients' seizures arose from N2 as is most typical of temporal lobe epilepsy,¹⁶ but polysomnography was not performed to evaluate how seizures may have affected overall sleep architecture and whether comorbid sleep pathologies such as sleep apnea, known to influence nocturnal seizure frequency, could have been present, although neither patient had reported clinically apparent symptoms of disruptive snoring, sleep disturbance, or excessive daytime sleepiness.

Limitations include very small numbers, lack of polysomnography, lack of detailed neuropsychological testing measures to specifically evaluate the clinical reports of ALF and RMI symptoms, and lack of formal posttreatment neuropsychological assessment. Also, although our patients endorsed that their memory problems resolved following seizure resolution, other factors are likely to be involved with the unique clinical syndrome of TEA and the distinctive phenomena of ALF and RMI, including bitemporal

pathology and sleep disturbance. Future larger studies of continuous video-EEG monitoring in patients with TEA will be necessary to confirm whether frequent nocturnal seizures may disturb sleep architecture and contribute to ALF and RMI.

ADDITIONAL CONTRIBUTORS

Dr. Burkholder—involvement in patient care, conceptualizing the study, drafting the manuscript, final approval. Dr. A. Jones and Dr. St. Louis—conceptualizing the study, drafting the manuscript, final approval. All other authors— involvement in patient care, critically revising the manuscript for intellectual content, final approval.

DISCLOSURE OF CONFLICT OF INTEREST

Drs. Burkholder, A. Jones, D. Jones, Fabris, Lagerlund, So, Worrell, and St. Louis report no disclosures. Dr. Britton is a coinvestigator for clinical trials sponsored by GW Pharma for cannabidiol in tuberous sclerosis epilepsy, and by Grifols for intravenous immunoglobulin in voltage-gated potassium channel complex antibody-associated epilepsy. Dr. Cascino is an investigator in the Human Epilepsy Project, receives technology royalties from Mayo Medical Ventures (high-frequency nerve stimulation to treat lower back pain, *Nervo*), and receives honoraria from the American Academy of Neurology and American Epilepsy Society. Dr. Shin is a coinvestigator for clinical trials sponsored by GW Pharma for cannabidiol in tuberous sclerosis epilepsy. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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