Case Report

"Benign" temporal lobe epilepsy with hippocampal sclerosis: A forgotten entity?

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ABSTRACT

Mesial temporal lobe epilepsy, a well-characterized epilepsy syndrome, is most commonly accompanied by the pathological feature of hippocampal sclerosis. Patients with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) typically present in childhood to early adolescence. We describe a cohort of patients who presented with their first epileptic seizure in late adulthood with atypical features. We characterized five patients with late-onset MTLE-HS by describing their demographics, electroclinical features, imaging, autoantibody status, and response to antiseizure medication (ASM) therapy. All five patients had their first seizure after the age of 50 with no history of initial precipitating incidents. None of our patients had positive serum or CSF autoantibodies and they have all remained seizure-free for a minimum of two years on ASMs alone. Two patients had motor vehicle crashes associated with seizures whilst three patients experienced seizures in sleep. A milder form of MTLE, previously described as benign TLE, does exist in routine clinical practice. These patients respond well to ASM therapy, but potentially harmful consequences such as motor vehicle crashes can occur in the untreated.
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1. Introduction

Temporal lobe epilepsy is the most common presentation of focal epilepsy in the adult population and is further classified into mesial and neocortical subtypes [1]. Mesial temporal lobe epilepsy is most frequently caused by hippocampal sclerosis which is characterized by atrophy and astrogliosis of structures such as the hippocampus, amygdala, parahippocampal gyrus, uncus and entorhinal cortex [2].

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) patients usually have a past history of initial precipitating incidents (IPIs) in childhood such as febrile seizures, perinatal hypoxia, head trauma, and intracranial infections [3]. There is a latent period of variable length between the IPIs and onset of the first epileptic seizure, but most patients present in childhood to early adolescence, typically between the age of four and 16 years [4]. One study showed that 88% of patients experience epileptic seizures before the age of 16 [5].

The classical seizure semiology in this cohort of patients can be described as focal seizures with impaired awareness which lasts for one to two minutes. There is typically an aura in the form of a rising epigastric sensation or psychic phenomena such as déjà vu, jamais vu, and fear. The aura is followed by behavioral arrest, oroalimentary or manual automatisms, and autonomic phenomena.

Approximately two-thirds of patients with classical MTLE-HS become drug-resistant [6]. Semah et al. found 10% of patients with temporal lobe epilepsy with hippocampal sclerosis were seizure-free on ASMs [7] whereas another study reported 42% of patients in remission for the past year [8] with 9.1 years being the average latent period between first epileptic seizure to being drug-resisant to ASMs [9].

Previous researchers have described a subgroup of MTLE patients identified as "benign MTLE" (bMTLE) presenting with late-onset and good response to ASM therapy [10]. In this report, we aim to describe a series of patients who presented with late-onset MTLE-HS. We characterize key features of this cohort including demographics, clinical presentation, seizure semiology, seizure control, EEG, and MRI findings to highlight the existence of this forgotten entity in routine clinical practice and its potential complications.

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Table 1
Detailed demographics, clinical details and investigations.

	Case 1	Case 2	Case 3	Case 4	Case 5
Demographics					
Age of first epileptic seizure	69	89	68	53	53
Sex	Male	Male	Male	Male	Female
Family Hx	Nil	Nil	Nil	14-year old son diagnosed with a childhood epilepsy syndrome – now seizure-free without ASMs	Mother diagnosed with idiopathic Parkinson's disease
Comorbidities	Nil	Nil	Benign essential tremor Chronic myeloid leukemia (developed 3 years after the diagnosis of epilepsy)	Nil	Chronic alcohol abuse
Clinical Details					
Risk factors for HS**	Nil	Nil	Nil	Nil	Nil
Seizure types	Focal to bilateral tonic-clonic seizures Focal impaired awareness seizures - auras (fearful expression & rising epigastric sensation)	Focal to bilateral tonic-clonic seizures	Focal impaired awareness seizures	Focal to bilateral tonic-clonic seizures	Focal impaired awareness seizures
Time from seizure to epilepsy diagnosis	Diagnosed after first seizure	Diagnosed after first seizure	5 years	6 months	4 months
ASMs	Levetiracetam Oxcarbazepine	Valproate	Phenytoin Levetiracetam	Carbamazepine	Valproate
Seizure-free period	2 years	2.5 years	4 years	3 years	4 years
Investigations					
MRI	Left hippocampal sclerosis	Bilateral hippocampal sclerosis	Bilateral hippocampal sclerosis	Right hippocampal sclerosis	Left hippocampal sclerosis
Routine EEG	Interictal sharp-wave discharges from the left temporal region VEM: focal impaired awareness seizures of left temporal onset	Normal EEG	Bilateral independent temporal epileptiform discharges Electroclinical seizure captured during EEG recording – seizure onset from left anterior temporal region	Right temporal sharp waves	Occasional bursts of left temporal delta slowing
Other imaging	CT chest, abdomen, and pelvis- no evidence of malignancy	CT chest, abdomen, and pelvis- no evidence of malignancy	CT chest, abdomen, and pelvis- no evidence of malignancy	Chest X ray- normal	CT chest, abdomen, and pelvis- no evidence of malignancy
Serum antibodies	Positive Nil Negative Anti-GAD Anti-NMDA Anti-VGKC Anti-neuronal antibodies	Positive Nil Negative Anti-AMPA Anti-CASPR2 Anti-DPPX Anti-GABA Anti-GAD Anti-IA2 Anti-LGI1 Anti-NMDA Anti-ZnT8 Anti-neuronal antibodies	Positive Nil Negative Anti-GAD Anti-NMDA Anti VGKC	Positive Nil Negative Anti-GAD Anti-NMDA Anti-VGKC	Positive Nil Negative Anti-GAD
CSF	Acellular with normal biochemistry Negative antibodies Anti-GAD Anti-NMDA Anti-VGKC Anti-neuronal antibodies	Nil	Nil	Nil	Acellular with normal biochemistry

Abbreviations: AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor, CASPR2 – contactin-associated protein 2, DPPX – dipeptidyl-peptidase-like protein 6, GABA – γ aminobutyric acid, GAD – glutamic acid decarboxylase, IA2 – islet tyrosine phosphatase 2, LGI1 – leucine-rich glioma inactivated 1, NMDA – N-methyl-D-aspartate receptor, VEM – video EEG monitoring, VGKC – voltage-gated potassium channel, ZnT8 – zinc transporter 8.
** febrile seizures, perinatal hypoxia, head trauma, and intracranial infections.

2. Methods

We retrospectively identified five patients with late-onset MTLE-HS who were followed-up by one of the authors (US) between February 2012 and May 2020. Data from medical records including clinical notes and pathology was collated and reviewed by the two authors. Imaging and EEG studies were re-reviewed for the purposes of this study. This study received approval from the Human Research Ethics Committee of Monash Health, Victoria, Australia.

3. Results

These five cases of late-onset MTLE-HS share several key characteristics, as summarized in Table 1, which we believe place them within the subset of bMTLE. Demographically, all our patients had their first epileptic seizure after the age of 50 with no past history of IPIs.

All five patients experienced focal impaired awareness seizures whilst three subjects reported focal to bilateral tonic-clonic seizures as well. Only one patient reported viscerosensory and psychic aura. Of note, three patients reported nocturnal seizures in sleep and one of them had seizures exclusively during sleep. Family members of four patients from our cohort reported subtle seizure activity characterized by oral and manual automatisms preceding the index seizure which led to medical attention.

Most of these patients had a prolonged latent period between the first seizure manifestation and the formal diagnosis of epilepsy with the longest period from our cohort being approximately five years. Additionally, two patients were diagnosed after motor vehicle accidents as a result of seizures during driving.

All of our patients were appropriately investigated with imaging studies, EEGs, and serum autoantibodies whereas one patient was further investigated with CSF analysis. MRI demonstrated hippocampal sclerosis in all patients while all serum and CSF autoantibodies returned negative. Three of the five patients demonstrated evidence of temporal interictal epileptiform discharges on EEG while electrographic seizures were captured in two. Intermittent temporal delta slowing and a normal EEG were seen in the remaining two cases.

All patients from our cohort remained seizure-free for at least 24 months after being commenced on the ASMs with three patients only requiring monotherapy and the other two being stable on combined therapy with two drugs.

Further clinical details of the five patients are summarized in Table 1. Figs. 1 and 2 demonstrate interictal and ictal abnormalities captured on the EEG of case number 3. A composite image of the coronal FLAIR and T1/T2 MRI images of all patients are presented in Fig. 3.

4. Discussion

These five cases represent a cohort of patients with atypical MTLE-HS and belong to the category of bMTLE described by researchers in the past [10].

The etiology of bMTLE is currently unknown, although, genetic factors are believed to be important [10]. This is in contrast to the classical MTLE-HS associated with IPIs which are acquired risk factors in early life such as febrile or prolonged seizures. Extrahippocampal epileptogenic lesions such as cortical malformations and low-grade tumors may coexist with HS in cases of dual pathology [3]. Additionally, central nervous system infections [3], parane-
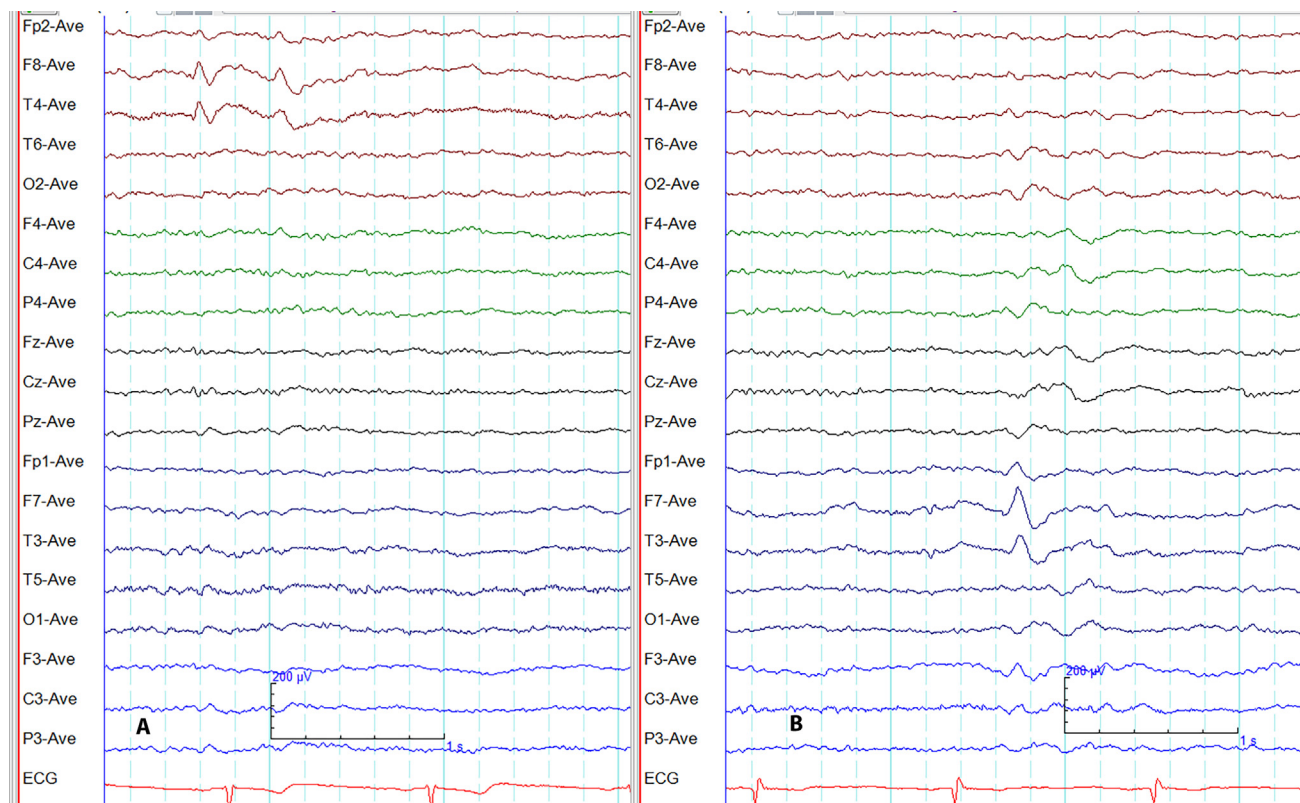

Fig. 1. Interictal epileptiform discharges (Case 3). Legend – Interictal epileptiform discharges involving (A) right temporal electrodes (F8, T4) and (B) left temporal electrodes (F7, T3). High-frequency filter = 70 Hz, Low-frequency filter = 0.5 Hz, Sensitivity = 10 µV/mm.
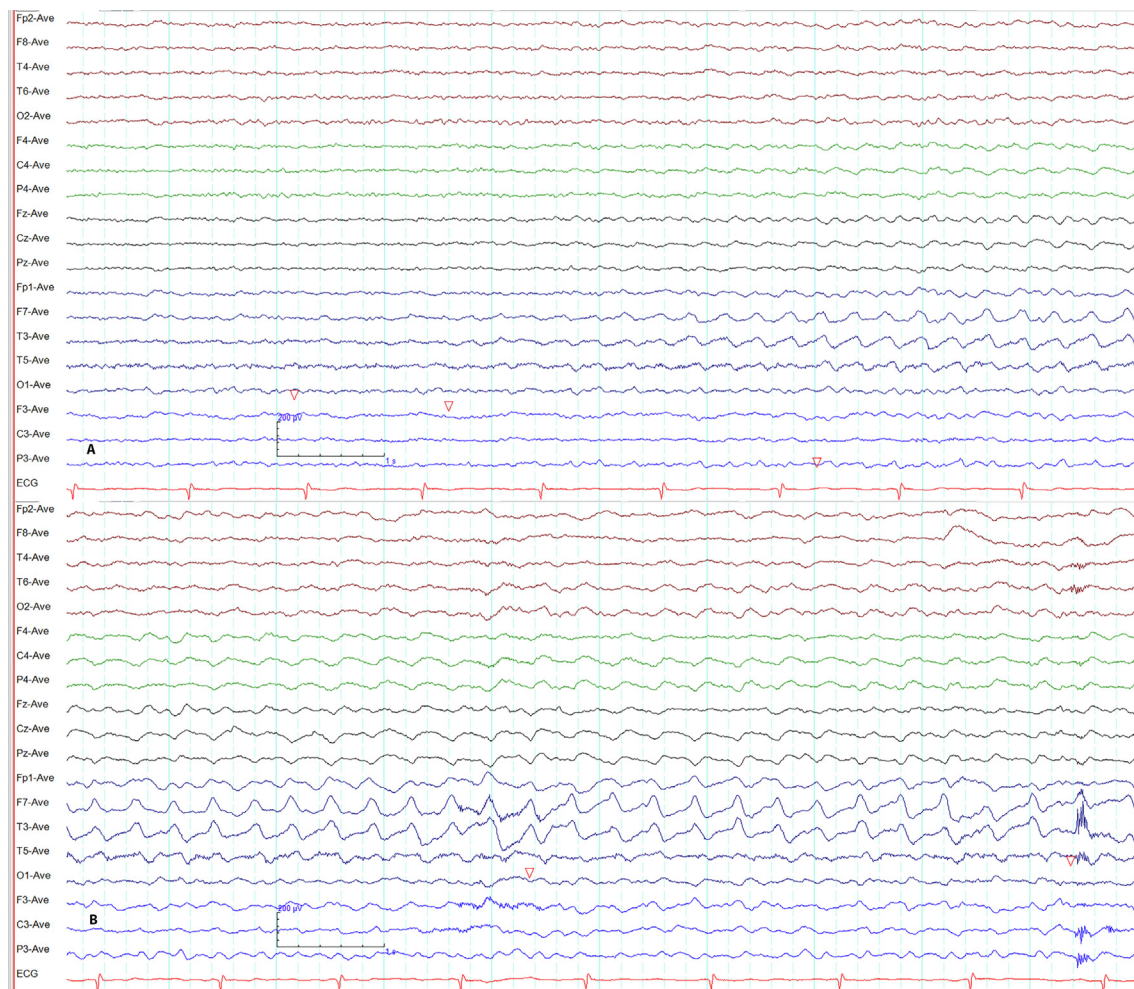
Fig. 2. Ictal EEG (Case 3). Legend – Note ictal onset with rhythmic theta activity over the F7, T3 electrodes (A), followed by an evolving ictal rhythm characterized by the increasing amplitude, decreasing frequency, and topographical spread (B). High-frequency filter = 70 Hz, Low-frequency filter = 0.5 Hz, Sensitivity = 10 μV/mm.

oplastic and autoimmune mechanisms [11] are other etiologies reported in MTLE-HS. However, none of our cases were found to be associated with any of these aetiological risk factors.

None of our cases had solid organ malignancies on initial screening with only one patient being diagnosed with chronic myeloid leukemia three years after the epilepsy diagnosis. We also investigated for the presence of autoantibodies given the more recent recognition of autoimmune-associated epilepsy [12]. On serum and CSF testing, no antineuronal autoantibodies were detected. This is in keeping with previous studies [13,14] which reported low rates of seropositivity of autoantibodies in patients with MTLE.

Given the lack of IPI in this cohort, it is important to identify risk factors associated with late-onset MTLE-HS. One retrospective study identified rheumatoid arthritis, autoimmune thyroid disease, and Lewy body disease pathology to be associated with a higher likelihood of HS in elderly patients above 90 years old [15]. Additionally, hippocampal sclerosis is seen among patients diagnosed with dementia. Based on autopsy studies, four to eight percent of subjects with dementia, including Alzheimer's disease and frontotemporal dementia, have HS [16]. None of our patients demonstrated evidence of comorbid autoimmune disorders or dementia, although no formal neuropsychiatric evaluation was undertaken. As bMTLE is often late-onset, the differentiation from dementia-

related HS can be a diagnostic challenge. However, there are radiological and neuropathological differences between the two groups. Hippocampal atrophy, loss of internal architecture, and T1/T2 signal abnormalities are the radiological hallmarks of HS common to both MTLE and dementias [4]. However, in MTLE, the extrahippocampal MRI changes involve the brain regions of the limbic system, whereas in Alzheimer's dementia, atrophy of the dorsolateral parietal-posterior temporal atrophy is typically seen [4]. MRI changes in Alzheimer's dementia tend to be bilateral more frequently than in MTLE. FDG-PET studies are further useful to make this distinction in which patients with Alzheimer's dementia typically demonstrate bilateral parietal hypometabolism whilst temporal hypometabolism, often unilateral, is seen in MTLE. In terms of neuropathology, neuronal loss and gliosis of CA1 region and subiculum are seen in both dementias and TLE [17]. However, severe involvement of the CA4 sector of the hippocampus is seen in MTLE only [17]. The disorganization and depletion of the granular cell layer can be seen in MTLE but is atypical for dementia-related HS [17].

With an increasing clinical and research emphasis placed on drug-resistant MTLE, the milder form of MTLE is largely forgotten. In 1971, Currie et al. reported a cohort of 666 TLE patients in which 19% had seizure-onset after 45 years of age and 33% experience mild and infrequent seizures [18]. Subsequent research identified
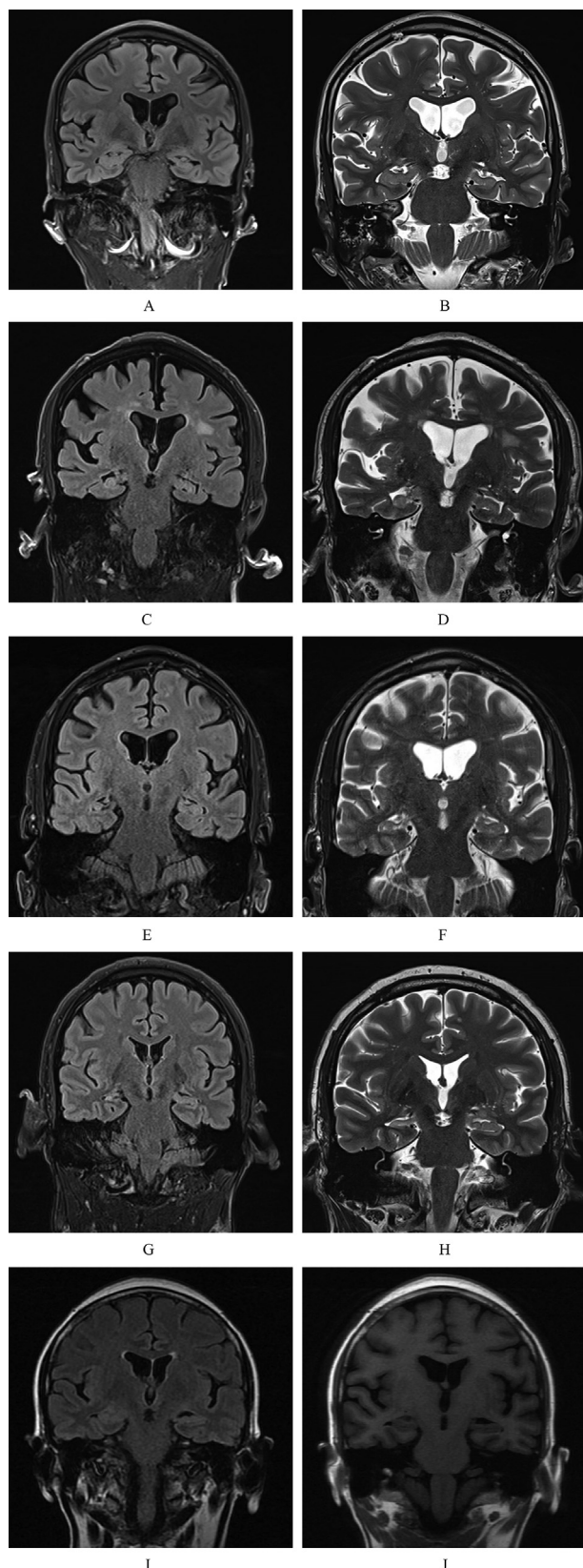
Fig. 3. Magnetic resonance images of Cases 1–5. Legend – Coronal FLAIR (A) and T2 (B) images of case 1 showing features of left hippocampal sclerosis. Coronal FLAIR (C) and T2 (D) images of case 2 showing features of right hippocampal sclerosis. Coronal FLAIR (E) and T2 (F) images of case 3 showing features of right hippocampal sclerosis. Coronal FLAIR (G) and T2 (H) images of case 4 showing features of right hippocampal sclerosis. Coronal FLAIR (I) and T1 (J) images of case 5 showing features of left hippocampal sclerosis.

this category as "benign MTLE". These patients typically present later than typical MTLE (mean age of onset 34 years), respond well to ASM therapy, run a milder course, and have HS on MRI in 39% [19,20].

Our case series demonstrate that despite being labeled "benign", bMTLE can still lead to dangerous and potentially fatal consequences such as motor vehicle accidents due to undiagnosed seizures, as was the case in two of our patients. The designation of the term "benign' to this entity and the mild nature of symptoms can provide patients and clinicians with a false sense of reassurance leading to sub-optimal ASM therapy and medical follow-up. The need for ASM therapy is further highlighted by the presence of nocturnal seizures in some patients which have been found to be a risk factor for sudden unexpected death in epilepsy (SUDEP) [21].

Thus, prompt recognition and early treatment of bMTLE can potentially result in better outcomes. Clinicians should be aware of the subtle auras like viscerosensory or psychic phenomena as well as infrequent focal aware and focal impaired awareness seizures which may be the only hint of this underlying epileptic disorder [10]. The difficulty in diagnosing this entity is further compounded by the fact that patients often have an unremarkable past medical history [10] and only 39% have HS on MRI [19,20]. Nocturnal and sleep-related seizures often go unrecognized as highlighted by three patients in our series. It is also worth noting that bMTLE can be misdiagnosed as psychiatric or gastrointestinal disorders with numerous non-diagnostic investigations [19].

Our study is limited by its retrospective design, incomplete serum and CSF testing, small cohort size, and the lack of detailed neuropsychological assessment. Seizures may overshadow the coexistent cognitive impairment, particularly if mild, unless specifically evaluated with neuropsychological tests as highlighted by previous case reports [22]. In retrospect, it would have been useful to follow up on these cases with serial neuropsychological testing to assess for potential progression to dementia.

In conclusion, our case series highlights the fact that a milder form of MTLE, previously described as bMTLE, does exist in routine clinical practice, though it has not received much limelight in the literature. Contrary to the previous literature, we emphasize that the course of this condition is not always benign due to the risk of undiagnosed seizures causing motor vehicle crashes and sleep-related seizures posing a potential risk of SUDEP. The diagnosis is often delayed as milder forms of seizures and nocturnal seizures are ignored or misdiagnosed until a major seizure or an accident draws medical attention. Increased awareness among clinicians and patients about this entity and its complications is necessary for early recognition, diagnosis and treatment in order to ensure better outcomes.

Author contributions

E.C.S.L.: literature search, data collection and interpretation, drafting and revision of manuscript. U.S.: study concept and design, literature search, data collection and interpretation, critical revision of manuscript.

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Ethical statement

We wish to confirm that this work has been carried out in accordance with the Declaration of Helsinki.

Disclosures

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

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