Nonlesional atypical mesial temporal epilepsy

Electroclinical and intracranial EEG findings

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ABSTRACT

Objective: Misleading manifestations of common epilepsy syndromes might account for some epilepsy surgery failures, thus we sought to characterize patients with difficult to diagnose (atypical) mesial temporal lobe epilepsy (mTLE).

Methods: We retrospectively reviewed our surgical database over 12 years to identify patients who underwent a standard anterior temporal lobectomy after undergoing intracranial EEG (ICEEG) evaluation with a combination of depth and subdural electrodes. We carefully studied electroclinical manifestations, neuroimaging data, neuropsychological findings, and indications for ICEEG.

Results: Of 835 patients who underwent anterior temporal lobectomy, 55 were investigated with ICEEG. Ten of these had atypical mTLE features and were not considered to have mTLE preoperatively. All of them had Engel class I outcome for 3 to 7 years (median 3.85). Five reported uncommon auras, and 3 had no auras. Scalp-EEG and nuclear imaging studies failed to provide adequate localization. None had MRI evidence of hippocampal sclerosis. However, ICEEG demonstrated exclusive mesial temporal seizure onset in all patients. Clues suggesting the possibility of mTLE were typical auras when present, anterior temporal epileptiform discharges or ictal patterns, small hippocampi, asymmetrical or ipsilateral temporal hypometabolism on PET, anterior temporal hyperperfusion on ictal SPECT, and asymmetry of memory scores. Histopathology revealed hippocampal sclerosis in 6 patients and gliosis in 2.

Conclusions: Atypical electroclinical presentation may be deceptive in some patients with mTLE. We emphasize the importance of searching for typical mTLE features to guide ICEEG study of mesial temporal structures in such patients, who may otherwise mistakenly undergo extramesial temporal resections or be denied surgery. *Neurology*® 2013;81:1848-1855

GLOSSARY

AED = antiepileptic drug; **ATL** = anterior temporal lobectomy; **FDG** = fluorodeoxyglucose; **HS** = hippocampal sclerosis; **ICEEG** = intracranial EEG; **IED** = interictal epileptiform discharge; **mTLE** = mesial temporal lobe epilepsy; **nTLE** = neocortical temporal lobe epilepsy.

Patients with mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS) often have medically refractory seizures but are considered excellent candidates for resective epilepsy surgery provided that they have unilateral disease. Typical MRI findings, coupled with concordant seizure semiologies, interictal and ictal EEG findings, and matching neuropsychological test profiles, usually provide sufficient evidence to support an anterior temporal lobectomy (ATL), which leads to excellent postoperative seizure outcome.¹ An intracranial EEG (ICEEG) evaluation may be indicated if there is MRI suspicion of bilateral HS and/or scalp-EEG evidence of bitemporal epileptogenicity,² or when noninvasive data provide discordant information.³ As in other epilepsy syndromes, the inherent limitations of a syndromic classification are well recognized.⁴ Given the high prevalence of mTLE, a degree of heterogeneity would be expected, and patients who do not conform to the typical mTLE-HS syndromic definition should not be overlooked. We sought to identify and characterize patients with intractable mTLE whose manifestations as

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a whole departed from the typical mTLE-HS characteristics defined by the 2004 ILAE (International League Against Epilepsy) Commission Report.⁵

METHODS See appendix e-1 on the *Neurology*[®] Web site at www.neurology.org for methods.

RESULTS Of the 835 patients that underwent ATL during the 12-year period from 1997 to 2008 at our institution, 55 were studied preoperatively with ICEEG. Preimplantation hypotheses for ICEEG were as follows (table 1):

1. Attempt to preserve the hippocampus in 14 patients (25.4%) with suspected dominant neocortical TLE (nTLE) and preserved verbal memory
2. Differentiate between mTLE and nTLE in 13 patients (23.6%)
3. Exclude a temporal onset in 8 patients (14.5%) with a preoperative hypothesis of frontal lobe epilepsy, in 9 patients (16.3%) with suspected parieto-occipital epilepsy, and 3 patients (5.4%) with suspected perisylvian-opercular epilepsy
4. Delineate the seizure onset zone in 6 patients (10.9%) with lesional nTLE
5. Define the side and extent of the seizure onset zone in 2 patients (3.6%) who had bitemporal ictal scalp-EEG patterns

Of the 2 groups (2–3), 10 patients with atypical electroclinical manifestations were surprisingly found to have an unequivocal mesial temporal seizure onset on ICEEG, and became seizure free for at least 3 years after a standard ATL.

Demographics. Patients' age at surgery ranged from 13 to 39 years (median 28). Onset of epilepsy was between 4 and 22 years (median 13) and duration of epilepsy before surgery ranged from 5 to 33 years (median 10.5). The group comprised 5 men and 5 women who had failed an average of 7 antiepileptic drugs (AEDs) before surgery. Seizure frequency varied from 1 to 70 seizures (median 9) per month. A family history of epilepsy was reported in one patient (P8). A probable initial precipitating injury was identified in 4 patients: 3 patients (P1, 2, 4) reported a history of isolated febrile seizures at the age of 6 months to 2 years, and one patient (P6) had a history of intracerebral hemorrhage of prematurity (grade II). All patients had a normal neurologic examination (table 1).

Seizure semiology. Auras were documented on video-EEG recording in 6 of 10 patients. One patient (P4) described an unexplained sensation in the lower abdomen, which was quickly superseded by a "tingling sensation" in the contralateral hand. Sensory

auras were present in 3 patients: one patient (P3) described a feeling of "warmth over the face and head" followed by tingling of fingers, one (P7) reported a sensation of nondiscrete body tingling with occasional "body feeling so hot," and another (P10) noted "going numb on the right side." A complex auditory aura, "hearing voices," was reported by one patient (P8). Visual auras characterized as "floaters" crossing over from the side, ipsilateral to the epileptogenic hemisphere was documented in one patient (P2). One patient (P5) reported déjà vu feeling in the past, which was not recorded during the 2 video-EEG evaluations. Two (P1, 9) of the 3 patients who never reported auras had dominant hemispheric epilepsy. All video-EEG-recorded seizures in one patient (P1) and $\geq 80\%$ of seizures in another 2 patients (P7, 10) occurred during sleep. Five patients (P2, 3, 5, 6, 8) had seizures exclusively during wakefulness. The first objective seizure manifestations were alteration of awareness without significant motor activity in 3, automatisms with impaired awareness in 4, complex motor phenomena (trembling, tossing/turning, bipedal movements) in 2 (P1, 9), and hyperkinetic manifestations with screaming and violent movements of the extremities in one patient (P7). Seizures subsequently evolved into face and/or arm tonic/clonic or head versive and generalized tonic-clonic seizures in 6 patients. Early motor semiology,⁶ tonic cry, and right face tonic seizures were seen in one patient (P8). Duration of recorded seizures ranged from one-half to 10 minutes (median 2.1). Four patients (P1, 2, 5, 10) had an average seizure duration of <1 minute (table 1).

Noninvasive electrophysiology. Absence of interictal epileptiform discharges (IEDs) was noted in 5 patients. Regional anterior temporal IEDs were seen in 5 patients, 3 of whom also had extratemporal IEDs involving the bifrontopolar (P7), frontocentral (P9), and parietal (P6) regions. Generalized and lateralized IEDs were documented in one patient (P9). Ictal EEG demonstrated primary activation of the anterior temporal region in 2 patients (P8, 10), the midtemporal region in 2 (P3, 5), and both regions in one patient (P4). The remaining 5 patients had mainly nonlocalizable and/or hemispheric patterns with or without temporal emphasis (table 1).

Pre- and postoperative structural imaging. Preoperative high-resolution brain MRIs with coronal magnetization-prepared rapid-acquisition gradient echo slices showed no identifiable abnormalities in 5, borderline small hippocampi in 3 (P3, 4, 10), ipsilateral smaller hippocampus in one (P5), and contralateral smaller hippocampus in one (P9). There was no hyperintense signal on fluid-attenuated inversion recovery/T2 in any of these patients. Postoperative MRIs indicated

Table 1 Patient demographics, seizure semiology, scalp video-EEG, imaging, and neuropsychology data, and preimplantation hypothesis

Patient	Age at surgery, y	Sex/ handed	Age at onset, y	Seizure semiology	Scalp-IEDs		Scalp-ictal EEG (amount)				Neuropsychology		Wada test/fMRI			
					Temporal	Extratemporal	Temporal	Extratemporal	MRI	PET	Ictal SPECT (injection)	IA/DA	IV/DV	Language	Memory (dominant)	Preimplantation hypothesis
1	37	M/L	4	CmS	anT	—	—	H (50%), NL (50%)	Normal	BL BI hypo (L > R) T	—	94/97 (Av/Av)	94/94 (Av/Av)	BL	L inj 9/9, R inj 4/9 (R)	L OFLE vs TLE
2	25	M/R	17	VsA ^a > DS > VS > GTC	anT	—	midT (40%)	H (27%), FL (22%), NL (11%)	Normal	BI hypo L neoT, FL	L poT, P (9 s)	59/64 (El/El)	71/72 (Bl/Bl)	L	L inj 10/12, R inj 8/12 (BL/R > L)	L POLE vs TLE
3	39	M/R	19	SA > DS > AS	—	—	midT	—	BL BI HP	BI hypo L neoT	—	99/108 (Av/Av)	103/97 (Av/Av)	L	L inj 5/9, R inj 8/9 (L)	L POLE vs TLE
4	30	F/R	21	AbA > SA > DS > GTC	—	—	anT, midT (71%)	—	BL BI HP	BI hypo L T, inFL, P	L anT, R T, BL anFL (28 s)	99/99 (Av/Av)	103/91 (Av/Av)	L	L inj 10/12, R inj 10/12 (BL)	L OpLE vs TLE
5	17	F/R	12	PcA ^a > AS	—	—	midT	—	Ipsi BI HP	BI hypo L neoT	—	114/105 (HA _v /HA _v)	118/118 (HA _v /HA _v)	L	L inj 9/9, R inj 9/9 (BL)	L nTLE vs mTLE
6	13	M/R	5	AS > CnS (L face/arm) > GTC	anT (65%)	P (35%)	—	TP (60%), NL (40%)	Normal	Mod hypo R midT, FL, Ins, P	—	87/88 (LAv/LAv)	54/66 (El/El)	—	—	R POLE vs TLE
7	31	F/R	5	SA > HmS > CnS (R face)	anT (95%)	BL FL (5%)	—	NL	Normal	BL BI hypo (L > R) T	L anT, L inFL (8 s)	71/80 (Bl/Bl)	103/94 (Av/Av)	L	L inj 4/12, R inj 8/12 (L)	L FLE vs TLE
8	22	F/R	9	AuA > AS > TnS (R face) > GTC	—	—	anT	—	Normal	BI hypo L T, inFL, inP	—	92/97 (Av/Av)	97/97 (Av/Av)	—	—	L nTLE vs mTLE
9	30	F/R	22	CmS > GTC	anT (15%)	FC (25%), H (15%), Gen (45%)	anT (11%)	H (78%), NL (11%)	Con BI HP	BI hypo L T, OF	L anT (11 s)	74/74 (Bl/Bl)	100/100 (Av/Av)	L	L inj 7/12, R inj 11/12 (BL/L > R)	L FLE vs TLE
10	26	M/R	14	SA > AS	—	—	anT	—	BL BI HP	BL mod hypo (L > R) FT	—	97/99 (Av/Av)	100/94 (Av/Av)	—	—	L POLE vs TLE

Abbreviations: AbA = abdominal aura; an = anterior; AS = automotor seizure; AuA = auditory aura; Av = average; BL = bilateral; BI = borderline; CmS = complex motor seizure; CnS = clonic seizure; Con = contralateral; DA = delayed auditory memory; DS = dialeptic seizure; DV = delayed visual memory; El = extremely low; FC = frontocentral; FL = frontal lobe; FLE = frontal lobe epilepsy; fMRI = functional MRI; Gen = generalized; GTC = generalized tonic-clonic; H = hemispheric; HAv = high average; HmS = hypermotor seizure; HP = hippocampus; hypo = hypometabolism; IA = immediate auditory memory; IEDs = interictal epileptiform discharges; in = inferior; inj = injection; Ins = insula; Ipsi = ipsilateral; IV = immediate visual memory; LAv = low average; mid = middle; mod = moderate; mTLE = mesial temporal lobe epilepsy; neo = neocortex; NL = nonlocalizable; nTLE = neocortical temporal lobe epilepsy; OF = orbitofrontal; OFLE = orbitofrontal lobe epilepsy; OpLE = opercular epilepsy; P = parietal lobe; PcA = psychic aura; po = posterior; POLE = parieto-occipital lobe epilepsy; SA = sensory aura; T = temporal lobe; TnS = tonic seizure; VS = versive seizure; VsA = visual aura.

The italic font highlights features that suggested mesial temporal involvement.

^aBased on history.

that the anterior temporal region and amygdalo-hippocampal complex had been resected in all patients (table 1).

Preoperative nuclear imaging. Mild bitemporal hypometabolism was noted in 2 patients (P1, 7) and moderate bifrontotemporal hypometabolism in one patient (P10). Two patients (P3, 5) showed subtle ipsilateral temporal neocortical hypometabolism. One patient (P6) had multiple ipsilateral nonadjacent hypometabolic areas. Ipsilateral frontotemporal hypometabolism with or without parietal lobe involvement was found in the remainder of patients. An ictal SPECT was accomplished in 4 patients. The injection time ranged from 8 to 28 seconds after EEG seizure onset. Ictal hyperperfusion involving the ipsilateral temporal lobe was identified in one patient (P9). The others (P2, 4, 7) demonstrated multiple areas of hyperperfusion in temporal, bifrontal, and parietal lobes (table 1).

Neuropsychological assessment. Of the 9 patients with left mTLE, 2 patients (P7, 9) had significantly lower auditory compared with visual memory index scores before surgery. The one patient with right mTLE (P6) had significantly lower visual than auditory memory performance (table 1).

Intracarotid amobarbital (Wada) tests. Seven of the 10 patients underwent Wada testing. Six patients were left-hemisphere dominant for language, and 2 patients (P3, 7) were also left-hemisphere dominant for memory, whereas 4 patients had bilateral memory representation. One patient (P1) with left-handedness had bilateral dependent language and right hemispheric memory dominance (table 1).

Pathology. Histopathology revealed HS in 6 patients, gliotic changes in the hippocampus in 2 (P3, 5), and nonspecific changes in one patient (P7). No adequate hippocampal tissue was submitted for analysis in one patient (P4) (table 2).

Invasive electrophysiology. We recorded 1 to 5 clinical seizures per patient (median 3). Three patients also had subclinical seizures. The seizure onset as defined by depth electrodes revealed a localized EEG seizure pattern (range 1–4 contacts, median 2.5) consistently arising from the hippocampus in all patients. Typical hippocampal seizure patterns⁷ were seen in most seizures. Additionally, the seizure onset involved the amygdala in 4 patients (P2, 3, 4, 8), and the parahippocampal gyrus in 2 (P5, 6) (table 2).

Surgical outcome. No postoperative complications were reported in this cohort. The follow-up period

Table 2 Electrode placement, results of ICEEG, surgical pathology, and outcome

Patient	Side	Subdural grid electrode placement (no. of contacts)	Depth electrode placement (no. of contacts)	Total no. of contacts (subdural/depth)	ICEEG-IEDs (amount)	ICEEG-ictal onset (amount)	Pathology	Operation/outcome ^a
1	L	latF (24), OF (16), bsT (18), neoT (48)	AM (8), anHP (8), poHP (8)	106/24	1. HP (80%); 2. neoT (17%); 3. meT (3%)	HP (5CS + SCS)	HS	L ATL/class IA at 3.9 y
2	L	latF (24), OF (16), bsT (12), neoT (40)	AM (8), anHP (8), poHP (8)	92/24	1. AM & HP (60%); 2. neoT (40%)	AM & HP (3CS + SCS)	HS	L ATL/class IB at 3.8 y
3	L	latF (40), OF (16), bsT (18), neoT (24), latP (12)	AM (8), anHP (8), poHP (8)	110/24	AM & HP	AM & HP (4CS + SCS)	Gliosis	L ATL/class IA at 6.1 y
4	L	latF (52), OF (16), bsT (12), neoT (30)	AM (8), anHP (8), poHP (8)	110/24	AM & HP	AM & HP (3CS)	NA	L ATL/class IA at 6.1 y
5	L	latF (12), OF (16), bsT (18), neoT (44)	AM (8), anHP (8), poHP (8)	90/24	1. bsT (55%); 2. meT (40%); 3. neoT (5%)	HP & PHG (5CS)	Gliosis	L ATL/class IA at 7.2 y
6	R	latF (40), bsT (12), neoT (44)	AM (8), anHP (8), poHP (8), PrCG (8), PoCG (8), neoT (8)	96/48	1. PHG (60%); 2. PoCG (30%); 3. inP (10%)	HP & PHG (1CS)	HS	R ATL/class IA at 7 y
7	L	latF (56), OF (16), bsT (18), neoT (44), latP (24), meF (12), meP (10)	anHP (8), poHP (8)	180/16	1. OF (73%); 2. meT (12%); 3. MTG & ITG (12%); 4. bsT (3%)	HP (3CS)	NS	L ATL/class IA at 3.8 y
8	L	latF (32), OF (16), bsT (12), neoT (24), meF (12)	anHP (8), poHP (8), ls (10)	96/26	1. suT (60%); 2. inF (20%); 3. OF (10%); 4. meT (5%); 5. bsT (5%)	AM & HP (3CS)	HS	L ATL/class ID at 3.6 y
9	L	latF (44), OF (16), bsT (12), neoT (48)	AM (8), anHP (8), poHP (8), SFG (10)	120/34	1. anT (80%); 2. PrCG (10%); 3. HP (4CS) MFG (5%); 4. OF (5%)	HP (4CS)	HS	L ATL/class IA at 3.3 y
10	L	latF (40), OF (16), bsT (12), neoT (48), meF (12), latP (48), meP (22)	anHP (8), poHP (8)	198/16	AM & HP	HP (1CS)	HS	L ATL/class IA at 3.3 y

Abbreviations: AM = amygdala; an = anterior; ATL = anterior temporal lobectomy; bs = basal; CS = clinical seizure; F = frontal lobe; HP = hippocampus; HS = hippocampal sclerosis; ICEEG = intracranial EEG; IEDs = interictal epileptiform discharges; in = inferior; ls = insular; ITG = inferior temporal gyrus; lat = lateral; me = mesial; MFG = middle frontal gyrus; MTG = middle temporal gyrus; NA = no adequate tissue; neo = neocortical; NS = nonspecific changes; OF = orbitofrontal; P = parietal lobe; PHG = parahippocampal gyrus; po = posterior; PoCG = postcentral gyrus; PrCG = precentral gyrus; SCS = subclinical seizure; SFG = superior frontal gyrus; su = superior; T = temporal lobe.

^aEngel classification.

after surgery varied from 3.3 to 7.2 years (median 3.85). Postoperative seizure outcome was examined using Engel classification.⁸ Scalp-EEG performed 6 months postoperatively revealed no IEDs in 8 patients. Two patients did not have follow-up EEG. At the most recent follow-up visit, 8 patients were completely free of seizures and auras (Engel class IA). One patient (P8) reported a probable generalized convulsion 8 months after surgery during inadvisable discontinuation of AEDs (class ID), but none since. One patient (P2) continued to report visual auras ("floaters"); however, these had never been recorded during presurgical video-EEG evaluations (class IB) (table 1). Epilepsy surgery allowed the AED regimen to be simplified in all patients. Two patients (P1, 4) were successfully withdrawn from all AEDs after 2 years. Five patients (P2, 3, 5, 6, 7) were on stable monotherapy. The remaining 3 patients were in the process of down-titrating AED dosages. Postoperative neuropsychological assessment was available in 6 patients. One patient (P6) who had undergone right ATL showed no change in memory scores after surgery. Of the 5 patients who had undergone left (dominant) ATL, 2 had verbal memory decline (P3, 5), and 3 patients (P2, 4, 8) maintained relatively stable memory performance over time (table 2).

DISCUSSION We report a series of 10 patients with medically intractable mTLE as confirmed by ICEEG recordings, histopathology, and postoperative seizure freedom for a minimum of 3 years who presented with atypical electroclinical manifestations suggestive of extramesial temporal seizure origin. In the majority of patients, habitual seizures either began with atypical or no auras and were associated with prominent motor manifestations or early progression to motor seizures. Scalp-EEG failed to provide adequate localizing information in most patients. None had clear radiologic evidence of HS on MRI or definite hypometabolism involving the mesial temporal region on PET. Ictal SPECT, neuropsychological assessment, and Wada test were generally nonlateralizing. These patients were considered to have nonlesional extramesial temporal epilepsy and were therefore studied extensively with ICEEG, targeting extratemporal regions. Nonetheless, there were some clues for mesial temporal epilepsy in each patient (highlighted in table 1 with the use of italics). Therefore, we also sampled from the mesial temporal structures to exclude their participation in seizure origin.

Seizure semiology reflects the functional properties of activated areas during seizure evolution. Multiple brain areas may be affected by the ictal discharges, and thus one clinical sign/symptom may obscure others, leading to false localization. Accordingly, the early involvement of extratemporal functional areas in

seizures arising from the mesial temporal structures would be dictated by underlying normal or aberrant cortico-cortical and cortico-subcortical connections. Sensory auras have been reported in 11% of patients with refractory TLE⁹ and only 6% of patients with mTLE.¹⁰ Given its proximity to the temporal lobe, the secondary sensory area (S2) located in the upper bank of the sylvian fissure may give rise to bilaterally indiscrete sensory phenomena, following propagation of mesial temporal seizures, as found in 2 of our patients (P3, 7). Unilateral paresthesia (P10) attributed to activation of the primary sensory area (S1) has been associated with contralateral temporal seizure onset.¹¹ Complex visual phenomena, visual distortion, particularly micropsia, have been described in TLE¹² whereas elementary hallucinations, e.g., flashing or moving lights (P2), are frequently seen in occipital seizures, but have been reported in up to 20% of patients with mTLE.¹³ The incidence of auditory auras in TLE varied greatly among different series from 1.7% to 16%.^{10,14} Elementary auditory phenomena and ringing or buzzing are frequently reported in nTLE and to a lesser extent in mTLE.¹⁵ Hearing voices, a complex auditory hallucination (P8), can be elicited by stimulation of the auditory association cortex situated in the superior temporal gyrus. Hyperkinetic seizures, characterized by violent and agitated motor behaviors involving mainly the proximal limbs and trunk (P7), have been reported in approximately 11% of patients with mTLE.¹⁶ Complex motor behaviors, characterized by natural movements similar to those executed during daily activities involving various body segments (P1, 9), can also be seen in patients with mTLE.¹⁷ Early elementary motor phenomena, simple motor seizures, suggestive of extratemporal onset or spread (P8), were observed in 8.6% to 12% of patients with TLE.¹⁸

Fifty percent of our patients had no detectable IEDs on scalp-EEG, and thus the irritative zone could not be defined. The absence or paucity of IEDs in TLE has been associated with a later age at seizure onset, less severe seizures, and lower incidence of hippocampal atrophy by MRI volumetry.¹⁹ Comparison of 64-channel scalp-EEG with stereo-EEG recordings demonstrated that even high-density scalp-EEG could not detect IEDs limited to the mesial temporal structures.²⁰ This phenomenon has been explained by the unique anatomical-physiologic characteristics of the amygdalo-hippocampal complex, comprising closed-loop electrical fields,²¹ and the distance separating scalp electrodes from the deep generator. Interestingly, extratemporal IEDs were found more often in patients with mTLE in the setting of tumors compared with HS.²² Generalized IEDs as found in P9 along with extratemporal IEDs (P6, 7) were frequently identified in children with mTLE-HS.²³ Disappearance of such IEDs (P6) after amygdalohippocampectomy or ATL may suggest

propagated IEDs intrinsic to epileptogenic circuits linking the temporal lobe to other areas. Ictal scalp-EEG patterns in unilateral mTLE tend to localize to the epileptogenic temporal lobe; however, up to 25% of patients with unilateral mTLE present with non-lateralizing²⁴ or widespread unihemispheric seizure patterns.²⁵ These nonlocalizing ictal scalp-EEG patterns were found in 50% of our patients. Rapid propagation of epileptic activity within the ipsilateral or even contralateral hemisphere is likely responsible for this observation.²⁶

On conventional MRI, HS is characterized by hippocampal atrophy and increased T2 signal intensity. It should be emphasized that MRI can be normal in a minority of patients with HS,²⁷ and thus unremarkable MRI as demonstrated in our entire cohort cannot entirely exclude the possibility of occult HS. Even quantitative MRI studies may not detect abnormalities, although microscopic examination of the hippocampus may reveal a mild degree of neuronal loss and gliosis limited to the hilus, known as “end-folium sclerosis.”²⁸ Recently, “paradoxical” TLE has been described in patients with normal MRI who have mTLE confirmed by long-term hippocampal recordings.²⁹ Hence, a continuum of mild sclerotic changes in the hippocampus is believed to exist without corresponding MRI abnormalities.

Our data of borderline ipsilateral temporal FDG-PET hypometabolism in 2 patients (P3, 5) are consistent with previous studies³⁰ in a minority of patients with mTLE in whom pathology confirmed the presence of HS. Uncommon areas of hypometabolism in intractable mTLE-HS have been found involving the ipsilateral extratemporal neocortices and contralateral temporal lobe³¹ as seen in 50% and 30% of our patients, respectively. Typical areas of ictal SPECT hyperperfusion in patients with mTLE with or without HS center in the anterior temporal region and extend contiguously to the insula and basal ganglia ipsilateral to the seizure onset zone.³² Atypical perfusion patterns have been associated with a more complex epileptogenic network and seizure propagation, diffuse seizure patterns, and timing of SPECT injection^{33,34} as shown in 2 of our 4 patients (P4, 7) in whom ictal SPECT was accomplished.

Although sampling bias is an inherent limitation of ICEEG, Engel class I outcome with a minimum follow-up of 3 years in all of our patients strongly suggests that the epileptogenic zone most likely resided within the resected temporal lobe that included the hippocampus, amygdala, and/or parahippocampus.³⁵ Nonetheless, the seizure generator in some cases might not have been purely restricted to the mesial temporal compartment, but may have extended to further resected and/or disconnected areas, including temporal neocortex, temporal pole (“mesiolateral or temporepolar”

subtype),³⁶ or neighboring structures, e.g., orbitofrontal cortex, insula, frontal and parietal operculum, or temporo-parietal junction (“temporal-plus epilepsy” subtype).³⁷ We observed a typical hippocampal seizure onset pattern⁷ in most seizures, without early ictal involvement in those adjoining networks that were extensively sampled. Although these EEG findings suggest that seizures did arise in the mesial temporal structures, the possibility of ictal propagation from areas that were not or insufficiently sampled cannot be excluded. We therefore do not suggest to focus the ICEEG evaluation on the mesial temporal areas in the absence of strong concordant clinical hints. Rather, we emphasize that patients similar to our cohort need comprehensive sampling from all candidate areas identified from noninvasive presurgical testing.

In nonlesional cases, mislocalization by clinical and electrographic findings can occur and raises a concern of unwary surgery.³⁸ “Pseudotemporal epilepsy” refers to a situation in which clinical and scalp-EEG findings suggest temporal lobe seizure origin, but seizures originate in extratemporal structures.³⁹ If unrecognized, this may lead to inappropriate temporal resection. Contrarily, our study describes a cohort that presented with atypical temporal or non-localizing electroclinical manifestations in whom the correct diagnosis and surgical strategy would have remained unclear without mesial temporal ICEEG exploration. We emphasize that mesial temporal sampling was not undertaken as part of a “routine” in these patients. Rather, some pieces of information from the presurgical evaluation pointed to the mesial temporal lobe in each patient. These include abdominal and psychic auras (or history of these), anterior temporal IEDs, regional temporal EEG seizure patterns, small hippocampi on MRI, (predominantly) ipsilateral temporal hypometabolism on PET, anterior temporal hyperperfusion on ictal SPECT, and finally significant asymmetry of memory scores (table 1). Accordingly, we suggest the term “pseudo-extratemporal epilepsy” for this cohort.

Atypical electroclinical features likely reflect aberrant seizure propagation beyond the temporal lobe⁴⁰ or more widespread epileptogenic networks, and thus have been associated with a poorer surgical outcome after ATL.³⁷ Nonetheless, extratemporal clinical features in these patients with mTLE-HS do not necessarily predict worse outcome after surgery.¹⁶ Our study reaffirms that atypical or extratemporal manifestations do not always indicate unfavorable surgical outcome even in patients with mTLE who do not have obvious HS. Inherent limitations of this study are its retrospective nature and ascertainment bias of reported cases, because we only included patients with atypical presentations who underwent epilepsy surgery with ICEEG sampling of the mesial temporal region.

This report formally describes a subgroup of patients with mTLE as confirmed by ICEEG, who presented with a constellation of electroclinical manifestations that depart from the “typical mTLE syndrome.”²⁵ Favorable surgical outcome may be attainable in such patients, when mTLE is confirmed by ICEEG evaluation, guided by a few clinical clues that may suggest mesial temporal lobe involvement during the presurgical evaluation.

AUTHOR CONTRIBUTIONS

Dr. Unnwongse contributed to conceptualization, data collection, interpretation, and drafting of the manuscript. Dr. Alexopoulos contributed to conceptualization, data interpretation, and revising the manuscript. Dr. Busch contributed to data interpretation and revising the manuscript. Dr. Wehner, Dr. Nair, and Dr. Bingaman contributed to revising the manuscript. Dr. Najm contributed to conceptualization and revising the manuscript.

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