Familial Lateral Temporal Lobe Epilepsy Confirmed With Intracranial Electroencephalography and Successfully Treated by Surgery
—Five Case Reports in One Family—

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Abstract

Documentation of familial epilepsy is of paramount importance for identification of epilepsy-associated genes, elucidation of pathomechanisms of epilepsy, and development of treatment of epilepsy. We report a Japanese family with 5 members with lateral temporal lobe epilepsy beginning around the second decade of life. All seizures were intractable to medical treatment, and four patients underwent surgical treatment following long-term monitoring by intracranial electroencephalography with subdural electrodes, which revealed neocortical origins for the seizure. These four patients were successfully treated with surgery. The clinical features of this familial temporal lobe epilepsy seem to be different from those of previously reported types of familial temporal lobe epilepsy.

Key words: temporal lobe epilepsy, epilepsy surgery, subdural electrode, familial epilepsy, autosomal dominant lateral temporal lobe epilepsy

Introduction

The etiology of temporal lobe epilepsy (TLE) is generally acquired, but familial TLE is also known.1 Familial TLE with autosomal dominant inheritance and incomplete penetrance has been increasingly recognized, and familial TLE has been included in the new proposal for the classification of epileptic syndromes by the International League Against Epilepsy.4 Two main syndromes have been identified based on seizure semiology, genetic background, and magnetic resonance (MR) imaging findings.

Autosomal dominant lateral TLE is characterized by juvenile-adult onset, rare seizures, and good response to antiepileptic medication. The main clinical feature is the recurrence of auditory symptoms during epileptic aura,16 suggesting a lateral temporal origin of the seizures. Less frequent ictal symptoms are visual, psychic, or aphasic seizures. MR imaging findings are usually normal and interictal electroencephalograms (EEGs) are usually unrevealing.13 Mutations causing autosomal dominant lateral TLE have been found in the LGI1/Epitempin gene.6,15 Mutations in coding regions or exon splice sites of the leucine-rich, glioma-inactivated 1 (LGI1) gene occur in about 50% of autosomal dominant lateral TLE families.12 Some rare families with drug-resistant autosomal dominant lateral TLE have been reported,2,7 but no previous patients have undergone intracranial EEG evaluation and surgical treatment because of the benign nature. However, the differential diagnosis between mesial and lateral TLEs based only on clinical features and noninvasive evaluation is often difficult.17

Familial mesial TLE was first described as a benign syndrome with prominent psychic and autonomic seizures, and no association with hippocampal sclerosis (HS) or febrile seizures (FS). More heterogeneous phenotypes with mild to severe epileptic disorders, and variable association with HS and FS have since been identified. The genetic characteristics of these conditions remain largely unknown.5,21 Refractory seizures may occur in up to 29% of patients.8 The medial temporal focus was identified in previous cases of familial mesial TLE based on the clinical semiology and scalp EEG.1 Only a few cases underwent intracranial EEG study covering both medial and lateral temporal regions.9

Here, we report a Japanese family with TLE that cannot be categorized into any of the reported forms of familial TLE. All five affected members had no apparent HS on MR imaging and four of the five affected members underwent successful surgical treatment because of refractory seizures. Subdural recording demonstrated the seizures originating from the lateral temporal neocortices.

Patients and Methods

Figure 1 shows the pedigree of the family. During treatment of the proband (Case III-1) and her mother (Case II...
II-1), we found that two more members of the family had epilepsy (Cases II-2 and III-2). Seizures were already refractory at that time in Case II-2, but his job prevented hospitalization. Repeated injuries and daily disability from seizures finally prompted him to seek surgical treatment after 10 years. Case III-2 had a less intractable course. He had been seizure-free for a while with medication of 800 mg of valproic acid, but the frequency of seizure gradually increased from several times per year to weekly after the age of 22 years, although clonazepam was added. Recently, gabapentin was tried but was ineffective, and now the effect of topiramate is being evaluated. Surgical treatment is also being considered. The fifth affected member (Case III-3) was a grandson of the grandfather of the proband and a different wife. He visited our clinic at the age of 38 years seeking surgical treatment of his refractory seizures. He and his family knew that some of their distant relatives had epilepsy, but their relationship was not close and so did not know that some of them had surgical treatment.

Intracranial recording with subdural electrodes used a trapezoid-shaped grid with four contacts aligned at the tip to detect the medial temporal activities in the first two patients (Cases II-1 and III-1). These contacts were placed at the same height with and just behind the tip of the dorsum sellae using fluoroscopy. This position enabled the four contacts to cover the parahippocampal gyrus in the anteroposterior direction. The lateral temporal cortices were covered with grid electrodes (Figs. 2B and 3B). More extensive areas were covered in the more recent two patients (Cases II-2 and III-3) (Figs. 4B and 5B). The medio-basal temporal region was covered with a trapezoid grid with 8 contacts aligned in a T-shape. The medial contacts were placed to cover the parahippocampal gyrus as with the early two patients.

Results

Table 1 is a summary of the clinical data of the affected five family members. Four patients had no history of febrile convulsion or other predisposing factors of epilepsy. No detailed past history could not be obtained for Case II-1, although she and her living relatives did not remember any previous episodes of convulsion, head trauma, or infection. The onset occurred around the second decade of life in all patients. Two patients reported no auras but the other three had numbness in the arm, tinnitus, or vertigo. The seizures were refractory to multiple antiepileptic agents in all patients.

MR imaging demonstrated no apparent HS in all five
Fig. 3 Case II-1, speech dominant on right, surgery on left. A: Electroencephalogram of habitual seizure. Bipolar leads of lateral temporal and parahippocampal subdural electrodes. Ictal discharges originated in the large area of the left lateral temporal cortex and immediately propagated to the right lateral cortex. Medial temporal areas were not involved in the early phase of the seizure. L.LAT and R.LAT: left and right lateral temporal cortices, respectively; L.PH and R.PH: left and right parahippocampal gyri, respectively. B: Schematic illustration of the positions of the electrodes, area of resection (shaded area), and multiple subpial resection (hatched area). Each circle represents the contact area of an electrode. Seizure started from the black circles.

Fig. 4 Case II-2, speech dominant on left, surgery on right. A: Electroencephalogram of initiation and propagation of a habitual seizure for 80 seconds. Monopolar leads of bilateral frontotemporal lateral neocortical and mediobasal temporal subdural electrodes. Ictal discharges started in the right lateral temporal neocortex (R.LT) with recruiting rhythm (arrowheads). The right parahippocampal gyrus (R.BT) was involved in the late phase of the seizure (arrow). L.BT and R.BT: left and right basal temporal cortices, respectively; L.F and R.F: left and right frontal cortices, respectively; L.LT and R.LT: left and right lateral temporal cortices, respectively. B: Schematic illustration of the positions of the electrodes, and area of multiple subpial resection (hatched area). Each circle represents the contact area of an electrode. Seizure started from the black circles.

patients. Case III-1 had a choroidal cyst on the contralateral side to surgical treatment. Case III-2 had a hippocampal sulcus remnant. Quantitative evaluation of the hippocampal volume and T2-weighted signal intensity in 3 patients found Cases III-1 and II-1 had mild laterality in hippocampal volume but not in signal intensity. The smaller side coincided with the seizure onset side. Positron emission tomography and single photon emission computed tomography found no specific findings in two patients, but the side of decreased uptake was concordant with seizure onset but was not within the ipsilateral mediolateral region in 2 patients.

The seizures in Case III-1 started from the left superior temporal gyrus with initial suppression and recruiting rhythm without involvement of medial temporal electrodes (Fig. 2A). She underwent anterolateral temporal
Fig. 5 Case III-3, speech dominant on bilateral, surgery on left. A: Electrocerricogram. Monopolar leads of bilateral frontotemporal lateral neocortical and mediobasal temporal subdural electrodes. Ictal discharges started in the left fusiform gyrus (L.BT and L.postBT) with polyspikes followed by suppression and recruiting rhythm (arrowheads). The seizure activity propagated to the left parahippocampal gyrus (L.PH) after 10 seconds (arrow). L.antBT and R.antBT: left and right anterobasal temporal cortices, respectively; L.BT and R.BT: left and right basal temporal cortices, respectively; L.latFT: left lateral frontotemporal cortices; L.PH and R.PH: left and right parahippocampal gyri, respectively; L.postBT and R.postBT: left and right posterobasal temporal cortices, respectively; R.Broca: right frontal cortex; R.latT: right lateral temporal cortex. B: Schematic illustration of the positions of the electrodes, and area of multiple subpial resection (hatched area). Each circle represents the contact area of an electrode. Seizure started from the black circles.

resection including 5 cm from the temporal tip, preserving the hippocampus and parahippocampal gyrus, and additional posterior corticectomy of the superior and middle temporal gyri with a 2-cm margin from the edge of the resection, and multiple subpial transection (MST) on a further posterior 2 cm of those gyri (Fig. 2B). Histological examination of the resected specimen found no abnormalities, and no gliotic, dysplastic, or neoplastic signs. She had several seizures within the first 3 years after surgery but has since been seizure-free for 7 years.

The subclinical seizures in Case II-1 originated from and were restricted to each side of the lateral temporal cortices at almost equivalent frequency after antiepileptic medication was stopped. Habitual seizures under medication originated from a considerably large area of the left lateral temporal cortex (Fig. 3A). Neither parahippocampal electrode detected any seizure origin or active interictal discharges. She underwent left anterolateral temporal resection preserving the hippocampus and parahippocampal gyrus. The anterior 5 cm of the lateral neocortices were removed and MST was added on a further posterior 2 cm of the superior temporal gyrus (Fig. 3B). Histological examination of the resected specimen found no abnormalities and no gliotic, dysplastic, or neoplastic signs. The seizures decreased significantly after surgery but persisted, so carbamazepine was added to the regimen 1.5 years after surgery. She continued to have several complex partial seizures per year for 8 years but has been seizure-free for the last 2 years.

The habitual seizures in Case II-2 originated from the posterior part of the right superior temporal gyrus, propagated in the right lateral temporal cortex, and then to the left lateral temporal cortex and the right mediobasal temporal regions (Fig. 4A). No seizure originated from the right mesial temporal area, but interictal spikes were recognized most frequently from the right parahippocampal gyrus, less frequently from the bilateral lateral temporal cortices, and rarely from the left parahippocampal gyrus. He underwent MST on the posterior part of the right superior temporal gyrus and anterior parts of the right middle and inferior temporal gyri. Intraoperative direct recording from the hippocampus revealed active discharges from the hippocampal head, so that multiple hippocampal transection and MST on the anterior parahippocampal gyrus were added (Fig. 4B). He returned to his job and has been seizure-free for 2 years.

The habitual seizures in Case III-3 originated from the inferior temporal neocortex, whereas interictal discharges were most frequently identified by the left parahippocampal electrodes, followed by the left lateral temporal electrodes. He underwent MST of the left middle and inferior temporal gyri and left fusiform gyrus. Intraoperative electrocorticography (ECoG) revealed absence of epileptiform discharges from these cortices but very active discharges persisting from the hippocampus, so that multiple hippocampal transection was added. He experienced transient mild language disturbance and memory decline which disappeared within one month. He returned to his job and has been seizure-free for more than 3 years except a single generalized clonic seizure episode at one year after surgery.

Only multiple transection procedures for both medial and lateral temporal regions without resection of the epileptic focus were performed in Cases II-2 and III-3. The rationale for this procedure is discussed later. Therefore, no pathological specimens were obtained from those two
<table>
<thead>
<tr>
<th></th>
<th>Case III-1</th>
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<th>III-2</th>
<th>II-2</th>
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<td><strong>Age (yrs)/type of seizure at onset</strong></td>
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<td>11/?</td>
<td>17/GC</td>
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<td>20/GC</td>
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<td><strong>Aura</strong></td>
<td>none</td>
<td>lt UE numbness</td>
<td>tinnitus</td>
<td>vertigo</td>
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<td><strong>Type and frequency of seizure</strong></td>
<td>weekly CPS, monthly SGS</td>
<td>weekly CPS, rare SGS</td>
<td>weekly CPS, SGS</td>
<td>daily SPS, weekly CPS, rare SGS</td>
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<td><strong>Antiepileptic agents used</strong></td>
<td>CBZ, ZNS, CZP, PRM</td>
<td>VPA, PR, PHT</td>
<td>VPA, CLB, GBP, CBZ*, PHT*</td>
<td>VPA, CBZ, ZNS, CLB</td>
<td>PHT, CBZ, VPA</td>
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<td><strong>Interictal spikes on scalp EEG</strong></td>
<td>bil mT</td>
<td>bil mT</td>
<td>rt mT, rare lt mT</td>
<td>rt mT, rt mT</td>
<td>lt at</td>
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<td><strong>MR imaging findings</strong></td>
<td>rt choroidal cyst</td>
<td>none</td>
<td>rt hippocampus sukus remnant</td>
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<td><strong>L1/lt hippocampal volume (mm³)</strong></td>
<td>3009/3466</td>
<td>2976/3403</td>
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<td>3724/3613</td>
<td>variability not performed</td>
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<td><strong>L1/lt abnormal signal intensity of hippocampus</strong></td>
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<td><strong>Nuclear medicine studies</strong></td>
<td>FDG-PET: np, ECD-SPECT: np</td>
<td>FDG-PET: mild decrease in lt mT</td>
<td>FDG-PET: mild decrease in lt mT</td>
<td>FDG-PET and IMZ-SPECT: decrease in lt mT</td>
<td>FDG-PET and IMZ-SPECT: decrease in lt mT</td>
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<td>VIQ74, PIQ84, FIQ74, no subjective memory decline</td>
<td>VIQ58, PIQ53, FIQ51, subjective memory decline</td>
<td>VIQ55, PIQ51, FIQ54, WMS-R: severe verbal memory decline</td>
<td>VIQ57, PIQ52, FIQ48, WMS-R: moderate verbal memory decline</td>
<td>VIQ57, PIQ52, FIQ48, WMS-R: moderate verbal memory decline</td>
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<td><strong>Age at surgery (yrs)</strong></td>
<td>18</td>
<td>43</td>
<td>46</td>
<td>38</td>
<td>38</td>
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<td><strong>Place of subdural electrodes</strong></td>
<td>bil parahippocampal, bil LT</td>
<td>bil parahippocampal, bil LT</td>
<td>bil parahippocampal and BT, bil frontaltemporal</td>
<td>bil parahippocampal and BT, bil frontaltemporal</td>
<td>bil parahippocampal and BT, bil frontaltemporal</td>
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<td><strong>Seizure onset</strong></td>
<td>lt T1</td>
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<td>Rt T1</td>
<td>lt T3 and T4</td>
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<td>anterolateral resection 5 cm, MST/none</td>
<td>anterolateral resection 5 cm, MST/none</td>
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<td>MST/hippocampus transection</td>
<td>MST/hippocampus transection</td>
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<td><strong>Pathology</strong></td>
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<td>unremarkable</td>
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<td>NA</td>
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<tr>
<td><strong>Follow up (yrs)</strong></td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>3</td>
<td>ug</td>
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<td><strong>Outcome</strong></td>
<td>class Ic: rare CPSs in first 3 yrs but no seizures thereafter</td>
<td>class Ic: rare CPSs for 8 yrs but no seizures thereafter (CBZ added at 1.5 yrs after surgery)</td>
<td>NA</td>
<td>class Ia: completely seizure free</td>
<td>class Ic: no seizure except single GCS at 1 yr after surgery</td>
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<td><strong>Postoperative neuropsychometry</strong></td>
<td>VIQ74, PIQ93, FIQ79</td>
<td>VIQ51, PIQ49, FIQ44</td>
<td>NA</td>
<td>VIQ70, PIQ64, FIQ64</td>
<td>VIQ58, PIQ69, FIQ59, WMS-R: no change other than marked improvement in visual memory</td>
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patients.

Discussion

A genetic background is strongly suspected for the aggregation of epilepsy in this Japanese family, since the clinical presentations were quite homogeneous and a common environmental background is unlikely in Case III-3 who grew up in a different family. The clinical features are apparently different from previously reported forms of familial TLE. The present cases of familial TLE are the first to be confirmed by intracranial EEG studies.

Recently four Japanese families with lateral TLE manifesting as the characteristic auditory features have been reported. Two different point mutations in the LG11 gene were identified in the two families, and were the first LG11 mutations in non-Caucasian autosomal dominant lateral TLE families. Such LG11 mutations in Japanese autosomal dominant lateral TLE families may not be uncommon, and diverse clinical phenotypes may make adequate diagnosis of autosomal dominant lateral TLE difficult based only on clinical information. Therefore, our family may represent a variant of autosomal dominant lateral TLE with a previously unreported mutation of the LG11 gene. Genetic analysis is now ongoing in our institute.

Since we did not place depth electrodes in the hippocampus, the possibility remains that seizures originated from a very limited area in the hippocampus but were not detected by subdural electrodes on the parahippocampal gyrus. However, this is unlikely based on previous studies that compared these two types of intracranial electrode. Hippocampal seizure activity detected by the depth electrodes was reflected in most mesial contacts of an inferior subdural strip. Misdiagnosis by subdural electrodes could occur but only if those electrodes were suboptimally placed, that is laterally to the collateral sulcus. In a previous study using simultaneous hippocampal depth and parahippocampal subdural recordings, the time lag between the seizure origin in the two electrodes was less than 5 seconds, which was shorter than the time lags in our patients.

The first two patients underwent surgical procedures limited to the lateral temporal neocortices, whereas the other two patients underwent procedures affecting both medial and lateral structures. One concern is whether the additional treatment to the medial temporal region was really necessary in the latter two patients. The change in our surgical protocol was based on the well-known complexity and poor surgical results of non-lesional TLE. Non-lesional TLE is notoriously associated with more extensive epileptic focus, complex involvement of both medial and lateral regions, and poorer surgical outcomes of conventional resective procedures. Limited resection is not enough to achieve seizure abolishment, so extensive resection is required that may endanger language and memory functions. Recently, we developed a non-resective procedure, or multiple hippocampal transection to the functioning hippocampus in non-lesional mesial TLE. This multiple hippocampal transection was developed originally to treat a medial temporal focus, but establishment of this procedure changed our surgical protocol for lateral TLE with no MR imaging abnormalities. Therefore, we used hippocampal transection to treat rapid seizure propagation to the medial region in chronic ECoG and residual prominently active epileptiform discharges from the hippocampus after treatment of the lateral epileptic focus in intraoperative ECoG, if the seizure origin was located in the basolateral or lateral temporal cortices. The efficacy of this protocol requires evaluation after long-term follow-up periods.

References


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