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厚生労働科学研究費補助金

障害者対策総合研究事業

MRIの補助に基づくFDG-PETによる局在関連性てんかん（部分てんかん）の術前焦点検索精度向上に関する研究

平成２２年度　総括研究報告書

研究代表者　高屋　成利

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目　　次

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MRIの補助に基づくFDG-PETによる局在関連性てんかん（部分てんかん）の術前焦点検索精度向上に関する研究

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研究要旨

現在の日本では、てんかん外科治療を受ける患者数は先進諸外国に比べて著明に少ない。毎年少なくとも 2000 人がてんかん外科治療を必要とすると推定されているにもかかわらず、実際に手術を受けることができているのは年間 500 人前後である。これは、英国や韓国の半分程度である。近年の神経画像をはじめとする診断技術の飛躍的進歩と手術手技の改良により、てんかんに対する手術治療の成果が国際的に確固たるものとなるにつれて、日本でも徐々にてんかん外科の重要性が認識されるようになってきた。このような時期に、低侵襲で、既に難治性てんかん焦点検索に対して日本国内で保険適応になっている FDG-PET の検査精度を向上させることは、難治性てんかん患者が手術を受ける機会を増加させることにつながり、患者個々人の健康回復に資するばかりではなく、将来の日本の就労人口の確保にとっても有用である。

この度の研究では、FDG-PET による異常検出部位を客観的かつ詳細に描出するとともに、MRI を補助的に用いることで、感度を保ったまま、特異度を高めることを今回の研究の目的とする。神経画像法によるてんかん焦点検索精度向上のためには、てんかん焦点そのものの研究のみならず、てんかん性放電伝搬に関する病態生理の解明が不可欠である。このような観点から、MRI の補助下で FDG-PET によるてんかん原性領域の検出感度および特異度を高めることを目的に、異常部位検出の客観的判断をするとともに、てんかん放電の伝搬に関する病態生理解明とそれによるてんかん焦点検出感度および特異を上昇させるための研究を、今年度は中心に行った。

その結果、てんかん性活動が伝搬すると想定される神経線維連絡特

異的に白質整合性低下が生じていることがあきらかになった。MRI 拡散強調画像を用いた FDG-PET によるてんかん焦点検出精度向上に役立つ可能性が高いと期待される。また、部分容積補正については、少なくともてんかんの種類によっては FDG-PET のてんかん焦点検出精度を向上させうることが示された。

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A．研究目的

てんかん外科手術による良好な発作コントロールを実現するためには、術前検査によるてんかん原性領域の正確な同定が不可欠である。FDG-PET は、このような難治性てんかんの焦点検索のための術前検査として 2002 年から保険適応となっている。FDG-PET は診療報酬点数 7,500 点の高価な検査であり、その有用性を高めることは医療資源の有効利用につながる。

FDG-PET は、MRI に比べて異常部位検出の客観的判断およびその解剖学的位置の同定が難しい。また、てんかん原性領域の検出感度は70－90%程度と高い反面、特異度が低く、擬陽性が多いのが難点である。そこで、FDG-PET による異常検出部位を客観的かつ詳細に描出するとともに、MRI を補助的に用いることで、感度を保ったまま、特異度を高めることを今回の研究の目的とする。

局在関連てんかんにおいては、てんかん焦点から発生したてんかん性放電は神経線維連絡によって周囲および遠隔領域に伝搬される。この伝搬により遠隔領域においてもてんかん性

放電や機能異常が描出されることは、正確なてんかん焦点検出を困難にしている一因でもある。そのため、神経画像法によるてんかん焦点検索精度向上のためには、てんかん焦点そのものの研究のみならず、てんかん性放電伝搬に関する病態生理の解明が不可欠である。

このような観点から、MRI の補助下で FDG-PET によるてんかん原性領域の検出感度および特異度を高めることを目的に、異常部位検出の客観的判断をするとともに、てんかん放電の伝搬に関する病態生理解明とそれによるてんかん焦点検出感度および特異を上昇させるために、今年度は以下の研究を実施した。

てんかん活動の伝搬に伴う投射神経線維の状態変化の評価：てんかん焦点と遠隔における機能低下領域間の神経連絡の描出の有無や同領域の拡散テンソルパラメータの測定によりてんかん性放電の伝搬による白質整合性の変化をしらべた。これにより、てんかん原性の有無が大脳白質に与える影響が明らかになれば、MRI 拡散強調画像を用いたてんかん原性病変の検出の補助に用いることができると考えている。

脳の局所的萎縮がもたらす部分容積効果によるブドウ糖代謝低下について評価：部分容積補正法を用いて、てんかん原性領域検出の特異度を上昇させることができるかについて、昨年度より検討して良好な結果を得た。異常部位検出の客観的判断をするために、空間的標準化により、健康被験者群と統計学的比較をすることで、恣意性を排除するために、年齢を患者とマッチさせた健康被験者データベースの構築を行った。これらの健康被験者データを利用して、独自の標準脳テンプレートを作成することで、空間的標準化の精度を上昇させる試みを行った。この方法により、近年提唱されている扁桃体腫大を伴う側頭葉てんかんの焦点検出精度を上げることを試みた。

B．研究方法

てんかん活動の伝搬に伴う投射神経線維の状態変化の評価については、

内側側頭葉てんかん患者 18 名および年齢および性別をマッチさせた健康被験者 18 名を対象として、FDG-PET スキャンおよび MRI 拡散強調画像および Magnetization Prepared Rapid Gradient Echo (MPRAGE) 画像の撮像を行った。まずは、標準脳上で患者群において健康被験者に比較してブドウ糖代謝低下の有る領域を検出した。これらの領域を側頭葉領域と側頭葉外領域に分離した。その上で、それらの領域を患者および健康被験者の個人脳に逆変換法によって移動して、これらの領域間の神経線維連絡を、MRI 拡散強調画像を FSL で解析することによって得られる確率的トラクトグラフィー法によって描出した。次に描出された神経線維を関心領域として、同領域の拡散テンソルを計算して、FA (fractional anisotropy) 値を求めた。

部分容積効果補正を行うことで、FDG-PETによるてんかん焦点検出精度

向上を試みる研究に関しては、扁桃体腫大を伴う側頭葉てんかん患者のFDG-PETを対象とした。これまでに収集した正常被験者データとそれらを使って作成した独自の標準脳テンプレートを用いて、解剖学的標準化を行った。各被験者のMPRAGE画像をsegmentationして灰白質部分を抽出した後に、FDG-PETの解像度に合致するように点像分布関数を掛け合わせて平滑化した。FDG-PETの画像をこの平滑化された灰白質画像で除することで単位体積あたりのブドウ糖代謝を計算した。このように部分容積効果補正を行った患者データと年齢をマッチさせた正常被験者群データに空間的標準化を行った後に、ジャックナイフ検定法による統計学的解析を加えて、術前患者のブドウ糖代謝低下部位を描出した。今回は、扁桃体腫大を伴う側頭葉てんかん患者のFDG-PET解析をMPRAGE画像で補正した。

（倫理面への配慮）

本研究計画は、被験者の文書によるインフォームドコンセントを得たうえで、被験者の人権及び利益の尊重に留意して研究を行うものとする。

(1) 説明および同意の方法：

対象者には、研究内容、本研究への協力の同意および人権保護、プライバシー保護について文書および口頭により説明する。MRIとFDG-PETは、ともに日常診療で利用された安全性が確立された検査である旨説明する。また、FDG-PET検査での放射能被ばくは、健康診断で行われる胃透視の検査と同程度であるが、この程度の放射線被ばく1回のみでは、健康に対する実質的な影響はない旨説明する。本研究への参加については、患者本人と家族またはその代諾者の自由意志による「同意書」を得る。

(2) 参加の任意性および離脱の自由について：

本研究への参加は自由意思で決めることができること、不参加であっても不利益のないこと、いつでも参加の取り消しができること、日常の診断および治療に何ら相違のないこと、および本研究の結果が公表されることなどを説明する.

C．研究結果

てんかん活動の伝搬に伴う投射神経線維の状態変化の評価：健康被験者に比べて内側側頭葉患者においては、トラクトグラフィーで描出されたてんかん性放電の伝搬神経線維と想定される白質のFA値が低下していた（図1）。また、トラクトグラフィーで皮質脊髄路を参照領域として描出して、同領域のFA値も測定して、repeated measures ANOVAを実施した。その結果、グループ（内側側頭葉患者vs. 健康被験者）×神経線維（てんかん性放電の伝搬線維 vs. 皮質脊髄路）に統計学的に有意な交互作用が認められた（図2）。

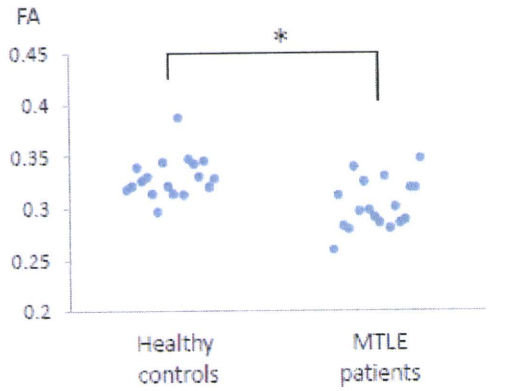

図１：てんかん性放電伝搬線維と想定される白質の整合性の変化。

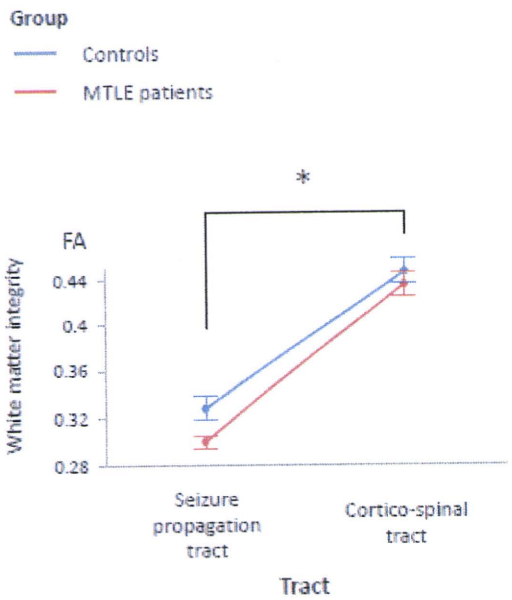

図２：内側側頭葉患者および健康被験者における、てんかん性放電の伝搬線維と皮質脊髄路での白質整合性の変化（平均値±標準偏差）。

患者個人の FDG-PET 画像の統計学的解析を、部分容積補正を併用することよって、FDG-PET のブドウ糖代謝低下領域検出の精度が上昇するか否かについての検討している。図３の症例では、部分容積補正前にはてんかん焦点の扁桃体以外にも側頭極や前頭葉内側などにも広範にブドウ糖代謝低下が検出されている。一方、部分容積補正後には検出されたブドウ糖代謝低下領域が減少して、側頭葉については扁桃体のみとなっている。

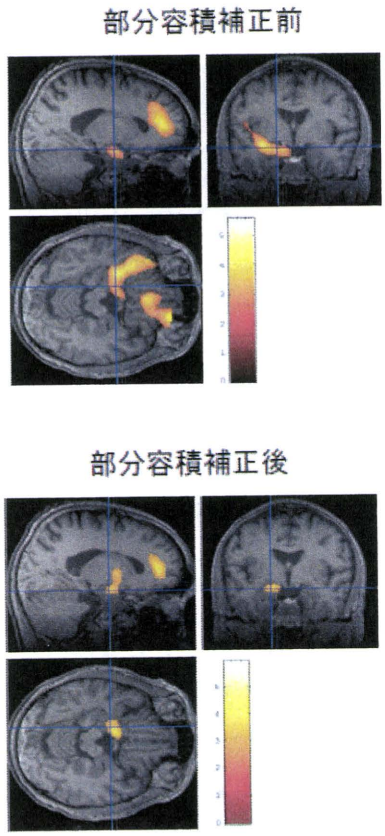

図３：部分容積効果補正による FDG-PET のブドウ糖代謝低下検出部位の変化

D．考察

てんかん活動の伝搬に伴う投射神経線維の状態変化の評価：内側側頭葉

てんかん患者においては、全脳の白質整合性の低下が存在することが報告されている。今回の結果は、このような白質整合性の低下は、てんかん性放電の伝搬経路に特異的に強く表れることが示唆された。今後更に、てんかん原性領域からの距離に依存して白質整合性の低下が強くなることが明らかになれば、MRI 拡散強調画像による FDG-PET のてんかん焦点検出精度向上につながるものと考えられ期待される。

部分容積効果補正については、扁桃体腫大を伴う内側側頭葉てんかんにおいては、FDG-PET によるてんかん焦点検出の特異度を上昇させうることが示された。

E．結論

てんかん性活動が伝搬すると想定される神経線維連絡特異的に白質整合性低下が生じていることがあきらかになった。MRI 拡散強調画像を用いた FDG-PET によるてんかん焦点検出精度向上に役立つ可能性が高いと期待される。

部分容積補正については、少なくともてんかんの種類によっては FDG-PET のてんかん焦点検出精度を向上させうることが示された。今後、この方法がより効果を発揮する症例選択の検討が必要である。

F．健康危険情報

該当なし。

G．研究発表

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H. 知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得
該当なし。
2. 実用新案登録
該当なし。
3. その他
特記事項なし。

研究成果の刊行に関する一覧表

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Amygdalar enlargement in patients with temporal lobe epilepsy

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ABSTRACT

Objective The purpose of the study was to clarify the significance of amygdalar enlargement (AE) in patients with temporal lobe epilepsy (TLE) detected by MRI.

Methods 11 TLE patients (eight men, mean age 45.3 (SD 18.2) years) with AE treated at Kyoto University Hospital were studied. Clinical history, ictal semiology, EEG, fluorodeoxyglucose—positron emission tomography (FDG-PET), interictal single photon emission CT (SPECT) and MRI were investigated. Amygdalar volume measured by 3 T MRI and its laterality index (LI) were compared with the three other groups: normal controls, patients with partial epilepsy of non-TLE and mesial TLE with hippocampal sclerosis (HS).

Results Average age of onset was 39.8 years (SD 19.5). Eight had complex partial seizures and three had generalised seizures. Epileptiform discharges were found in the temporal area ipsilateral to the AE by EEG. Interictal FDG—PET/SPECT revealed regional hypometabolism or hypoperfusion in the ipsilateral temporal area. MRI showed AE on the right in five patients, on the left in five and bilateral in one, all without apparent HS. Ten of 11 patients were diagnosed as unilateral TLE ipsilateral to the AE by neurophysiological and neuroimaging methods. Enlarged amygdalae showed iso- to slightly high intensity in FLAIR images without enhancement. Unilateral AE was not seen in the other three groups for amygdalar volume and LI ($p<0.05$).

Discussion AE is most likely a subtype of TLE without ipsilateral HS. This possibility of AE should be considered in TLE patients if there is no apparent HS.

INTRODUCTION

Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) is a well defined epileptic syndrome. The amygdala, which is a part of the limbic system, may play an important role in the epileptogenicity of patients with MTLE with HS.[1–3] In neurophysiological studies using intracerebral recordings, 5% of MTLE patients had seizure onset in the amygdala.[4] In previously reported imaging studies, isolated unilateral amygdala damage determined by either reduced volume or prolonged T2 relaxation time was observed in 8% of MTLE patients.[5] Therefore, the amygdala may not only be involved and affected in MTLE but may also be regarded as an independent cause of MTLE. The amygdala is decreased in volume by at least 20% in 19% of temporal lobe epilepsy (TLE) patients.[6] Recently, amygdalar enlargement (AE) was observed in 4% of intractable TLE patients.[7] Accounting for laterality of the amygdala,[8] AE could be an epileptogenic focus. However, a role for the amygdala as a focus of epilepsy has not been explicitly established, unlike hippocampal epilepsy.

The main purpose of this study was to clarify the clinical significance of AE in patients with TLE detected by MRI. The occurrences of AE were compared with other partial epilepsies such as non-TLE and typical MTLE with HS as well as with normal controls. One of the patients (Patient 2) was shown previously as a case report.[9]

METHODS

Subjects

Subjects were 11 MTLE patients with AE (mean age 45.3 (SD 18.2) years) treated at Kyoto University Hospital from 2003 to 2007 (AE group). MTLE with AE was diagnosed by the presence of complex partial seizures (CPSs) and by 1.5 T MRI and conventional scalp EEG, as described below. MRI indicated AE in all patients, as determined by the assessment and agreement of two neurologists. The volume of the amygdala was finally measured by 3 T MRI, as described below. Patients in whom there was a high suspicion of tumorous disease where the enlarged amygdala apparently compressed the adjacent tissue or showed clear intensity changes in T2 weighed or FLAIR images were excluded. Patients with dual pathologies were also excluded from the study. Routine EEG in 10 patients indicated focal epileptiform discharges predominantly in the temporal area ipsilateral to the AE. Fluorodeoxyglucose—positron emission tomography (FDG-PET) or single photon emission CT (SPECT) was also performed to support the clinical diagnosis. Localisation of the epileptogenic focus was determined by taking into account clinical semiology, EEG, conventional neuroimaging studies such as 1.5 T MRI, and FDG-PET/SPECT. Time from the first seizure to the date of the present study was at least 1 year.

As a comparison for amygdala volume, 17 focal epilepsy patients who had focal epileptiform discharges except for the temporal area without structural lesion by 1.5 T MRI (non-TLE group, mean 27.1 (SD, 11.6) years), 15 MTLE patients with HS by 1.5 T MRI (MTLE+HS group, mean 29.7 (SD 13.9) years) and 14 healthy volunteers (normal group, mean 30.1 (SD 8.3) years) were also recruited from the subjects who underwent 3 T MR imaging study during the same period. The former two groups (ie, non-TLE group and MTLE+HS group) had 3 T MRI for volume analysis of the amygdala.

3 T MRI acquisition

For the eight patients with AE, as determined by conventional 1.5 T MRI, an MRI study was also performed with a 3 T MR scanner (Magnetom Trio; Siemens, Erlargen, Germany) with magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequences (repetition time (TR) 2000; echo time (TE) 4.4; time interval (TI) 990 ms; flip angle 8°; matrix 256×256; field of view 24 cm; 208 slices; slice thickness 1 mm; voxel size 0.9375×0.9375×1 mm; no interslice gap; signal averaging). Figure 1 shows a representative image of AE by 3 T MRI. All patients provided informed consent prior to 3 T MRI examination. Similarly, 17 patients from the non-TLE group, 15 patients from the MTLE+HS group and 14 normal volunteers underwent a 3 T MR imaging study during the same period.

Amygdalar volumetry

We measured amygdalar volume by counting the number of voxels in a manually outlined volume of interest (VOI) on the MPRAGE images based on Cavalieri's method. VOI was manually drawn on the three dimensional MPRAGE image using MRICro (V.1.39, Roden, 2005). The amygdala was traced by a single rater (TM) using the method described in a previous study and also based on an atlas based approach.[10 11] An example of a VOI is shown in figure 2. Anatomical borders were adopted from previous studies.[8 12–14] Adjacent structures such as the putamen, hippocampus and parahippocampal gyrus were carefully excluded.

Statistical analysis of amygdalar enlargement

Amygdalar volumes were statistically analysed by paired t tests to determine the laterality between the normal and abnormal sides for each patients (AE, non-TLE and MTLE+HS) and also analysed between the larger and smaller sides for the normal group. We also compared the laterality between the AE group, non-TLE group, MTLE+HS group and normal controls by volume and laterality index (LI=(larger side−smaller side)/(larger side+smaller side)). These analyses were performed using SPSS 14.0 (SPSS Inc. 2005).

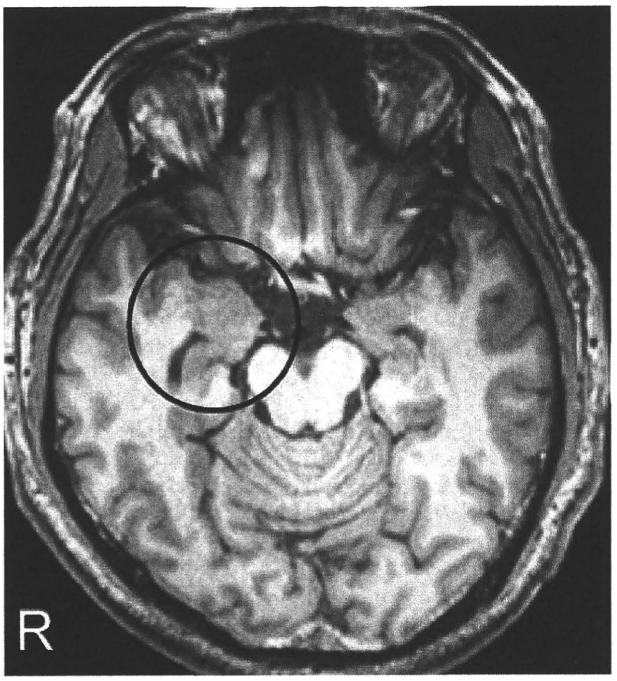

Figure 1 Axial T1 weighed MRI in patient No 9. Open circle indicates a representative image of right amygdalar enlargement. The intensity of the amygdala does not show laterality. No abnormal lesions were found in areas adjacent to the amygdala.

RESULTS

Clinical profiles of 11 patients

Patients included eight men and three women with an averaged seizure onset age of 39.8 years (SD 19.5). Two out of 11 patients had febrile seizures, eight had CPS and three had generalised tonic–clonic seizures. Two patients (patient Nos 2 and 9) felt anger and one patient (patient No 10) felt anxiety as their habitual psychic auras. Seizure frequency was at least once per month in 10 of 11 patients. Only one patient (patient No 3) had seizures once a year. Routine EEG in 10 patients indicated focal epileptiform discharges predominantly in the temporal area ipsilateral to the AE. For 10 patients, interictal FDG-PET/SPECT showed regional glucose hypometabolism or decreased regional cerebral blood flow in the ipsilateral temporal lobe. By 1.5 T MRI, AE was detected on the right in five patients, on the left in five and was bilateral in one. The enlarged amygdala showed iso- to slightly high intensity in 1.5 T FLAIR images but no enhancement by gadolinium. Mild HS ipsilateral to the enlarged amygdala was suspected in only one patient. Epileptogenic foci were ipsilateral to the AE in 10 patients with unilateral AE. One patient with bilateral AE (patient No 10) showed no laterality (table 1).

Valproic acid (mean dose 800 mg/day) was used in five patients and sufficient seizure control was obtained in four patients. Carbamazepine (CBZ) (mean dose 317 mg/day) was later given to nine patients, and eight patients became seizure free or showed a dramatic improvement in seizure occurrence.

Among 11 patients, one (patient No 1) had intractable seizures and underwent selective amygdalohippocampectomy and partial resection of the adjacent temporal lobe cortex guided by intraoperative electrocorticogram.[15] His seizures subsequently decreased (Engel's class II). A pathological study indicated hippocampal gliosis compatible with TLE and partial dysplasia in the right temporal tip. Only non-specific gliosis was found in the amygdala. Patient No 11 also underwent lesionectomy of the enlarged amygdala and became free from seizures after surgery (Engel's class I). A pathological study also indicated focal cortical dysplasia with mild gliosis in the left amygdala.

Follow-up 1.5 T or 3 T MRIs were performed in five patients (patient Nos 2, 5, 7, 8 and 9) 2–5 years after the first MRI. None showed further increased volume of the abnormal amygdala (no change in two and slight improvement in three).

Results of 3 T MRI amygdalar volumetry

Table 2 shows the amygdalar volumes of eight patients in the AE group determined by 3 T MRI. On the side of the AE with seizure focus, amygdalar volume ranged from 1333.3 mm^3 to 2011.8 mm^3 (mean 1700.1 (SD 285.0) mm^3). On the contralateral side, amygdalar volume was smaller and ranged from 957.8 mm^3 to 1658.5 mm^3 (mean, 1189.1 (SD 227.4) mm^3). There was a significant difference between the two sides ($p<0.05$, figure 3). In the non-TLE group (17 patients), amygdalar volume on the ipsilateral side to the seizure focus ranged from 773.2 mm^3 to 1270.6 mm^3 (mean 1028.4 (SD 158.1) mm^3) and that of the contralateral side ranged from 782.0 mm^3 to 1448.2 mm^3 (mean 1093.2 (SD 174.3) mm^3). There was a significant difference between the two sides ($p<0.01$, figure 3),

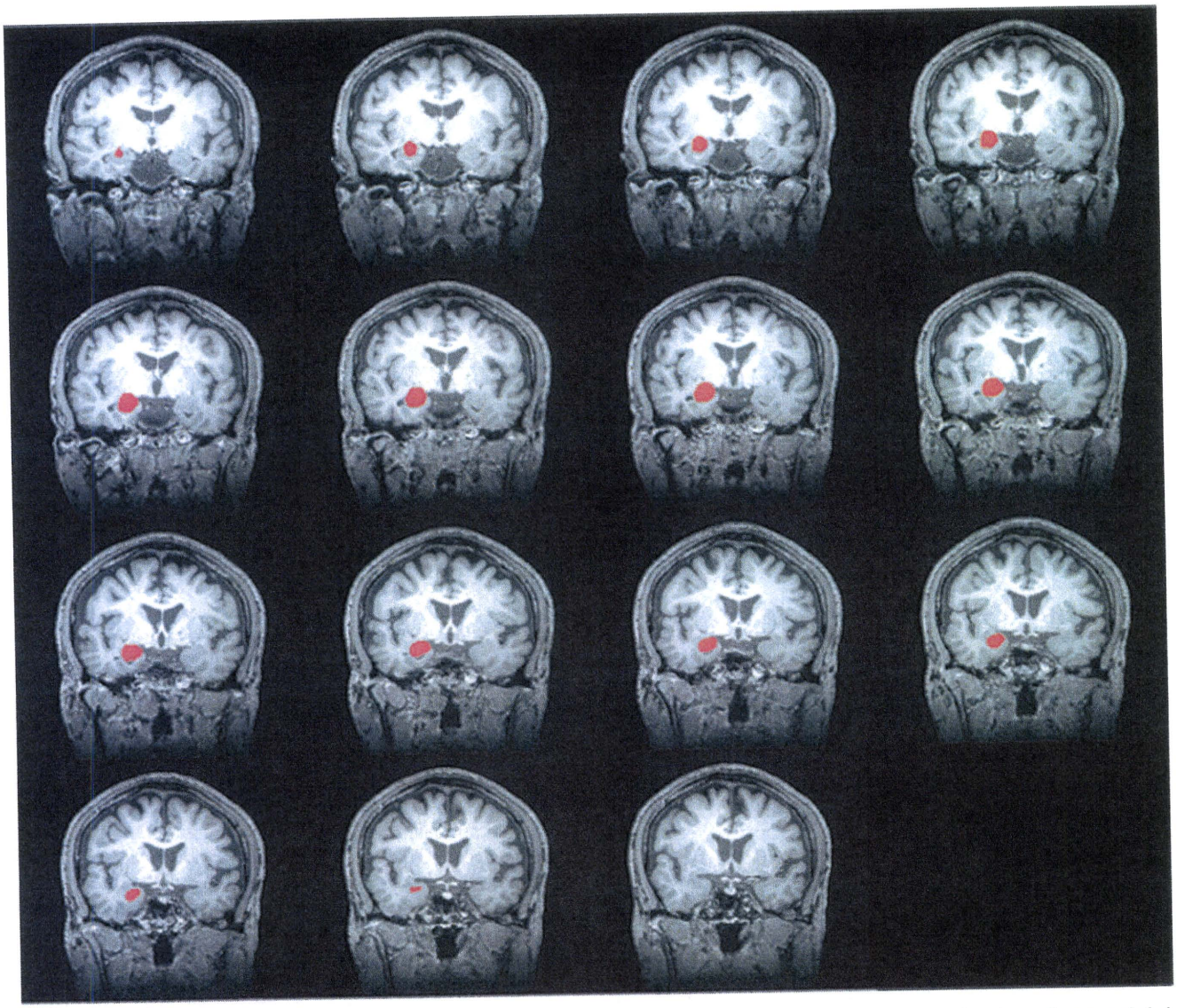

Figure 2 Volume of interests (VOIs) in the amygdala (patient No 2). VOIs are indicated in red. Hippocampal head and basal ganglia are excluded.

being smaller on the focus side. In the MTLE+HS group (15 patients), the amygdalar volume on the ipsilateral side to the seizure focus ranged from 778.5 mm^3 to 1293.6 mm^3 (mean 1060.4 (SD 150.9) mm^3) and that of the contralateral side ranged from 859.7 mm^3 to 1343.1 mm^3 (mean 1122.4 (SD 157.4) mm^3). There was a significant difference between the two sides ($p<0.01$, figure 3). Namely, both non-TLE and MTLE+HS groups showed a smaller amygdalar volume on the focus side in contrast with the AE group.

In normal subjects (14 patients), the left amygdalar volume ranged from 941.3 mm^3 to 1433.2 mm^3 (mean 1140.0 (SD 154.5) mm^3) and the right ranged from 998.4 mm^3 to 1342.2 mm^3 (mean 1152.6 (SD 108.4) mm^3). There was no significant difference between the two sides (not shown in figure 3). When they were grouped into smaller and larger sides, the smaller side ranged from 941.3 mm^3 to 1342.2 mm^3 (mean 1105.5 (SD 117.6) mm^3) while the larger side ranged from 998.4 mm^3 to 1433.2 mm^3 (mean 1187.7 (SD 134.9) mm^3). There was a significant difference between the two sides ($p<0.01$, figure 3).

Amygdalar volume of the affected side among the three patient groups and larger side in the normal group was compared, and it was the significantly largest in the AE group (one way ANOVA with post hoc test, $p<0.01$, figure 3).

When normal subjects were grouped into left and right sides (not shown in figure 3), there was no significant difference between the unaffected side of the AE group and either left or right side in normal subjects (not shown in figure 3). There was a significant difference between the affected side of the AE group and both the left and right sides in normal subjects ($p<0.05$, not shown in figure 3).

Among the three groups, except for the AE group, the affected side of MTLE+HS was significantly smaller than the larger side of the normal group ($p<0.05$, figure 3). There was no significant difference between the affected side of non-TLE and MTLE+HS (figure 3).

In terms of LI, LI of the AE group (0.176 ± 0.107) was significantly larger than that of the non-TLE group (0.036 ± 0.034), MTLE+HS group (0.028 ± 0.026) and normal controls (0.035 ± 0.025) (one way ANOVA with post hoc test, $p<0.05$, figure 4).

Table 1 Clinical profiles of the 11 patients

Patient No	Age at scan (years)*	Gender	Onset age	FS	Seizure type	EEG	Imaging studies†	Current medication and dosage‡	Seizure frequency§
1	21	M	9	–	CPS	R	R	VPA 1400, ZNS 225, CLB 5, CBZ 800	2/month
2	63	M	46	–	CPS	R	R	***CBZ 250***	Free
3	25	M	15	–	GTC	L	L	VPA 400, ***CBZ 400***	Free
4	24	F	19	–	CPS	L	L	PB 90, ***CBZ 200***	Free
5	57	M	49	–	CPS	L	L	VPA 600, ***CBZ 200***	Free
6	41	M	40	+	CPS	R	Not done	***CBZ 600***	2/year
7	32	F	32	+	GTC	L	L	VPA 800, ***CBZ 350***	Free
8	63	M	61	–	CPS	R	R	***CBZ 400***	Free
9	45	M	44	–	GTC	R	R	VPA 800, ***CBZ 200***	Free
10	74	F	72	–	CPS	R	Bilateral	***CBZ 50***	Free
11	53	M	51	–	CPS	L	L	***CBZ 200***, DZP 4	Free

*Patient age at the time of 1.5 or 3 T MRI examination. Mean age was 45.3 years (SD 18.2).
†Imaging studies consisted of interictal SPECT (single photon emission CT) and FDG-PET (fluorodeoxyglucose–positron emission CT).
‡Current medication is shown. Note that CBZ monotherapy or polytherapy with a relatively low dose of CBZ (written in ***bold, italic body***) improved seizure control.
§Seizure frequency after drug administration.
CBZ, carbamazepine; CLB, clobazam; CPS, complex partial seizure; DZP, diazepam; FS, febrile seizures; GTC, generalised tonic-clonic seizure; L, left; PB, phenobarbital; R, right; VPA, valproic acid; ZNS, zonisamide.

DISCUSSION

Amygdalar enlargement as a cause of TLE

MTLE is regarded as surgically remediable focal epilepsy characterised by hippocampal atrophy and sclerosis as the epileptogenic area. However, it has remained poorly understood how important the amygdalar body is in patients with MTLE or whether the amygdalar body per se plays a sole role in epileptogenicity.[2 3] The results of this study, in conjunction with previous electrophysiological and radiological studies, indicate that AE may function as an epileptogenic focus in subgroups of TLE patients.[9 16] AE was observed bilaterally in 16–18% of epilepsy patients with psychosis.[17] In contrast, significant amygdalar atrophy was seen in TLE patients with ictal fear[18] or affective aggression.[19] In previous studies,[20] the amygdaloid body was severely altered in TLE patients without HS and was smaller in volume compared with those analysed in the present study.

Concordant with a previous study, amygdalar volumes were smaller in the affected side of MTLE+HS and non-TLE patients in the context of conventional amygdalar sclerosis. In the present study: (1) we defined the clinical features of patients with TLE and AE and (2) we found that no AE was observed in patients with MTLE and HS, those with unilateral partial epilepsies other than TLE or in normal groups. Additionally, when we grouped normal data into larger and smaller sides of amygdala body, AE was significantly larger than in normal subjects. The AE group also showed a significantly larger LI among the other three groups. Namely, AE seems to be a specific phenomenon which can be observed in a certain subgroup of TLE patients. Moreover, we may consider a certain population of MTLE to have an epileptogenic focus in the amygdala, especially when the amygdala is enlarged.

Table 2 Comparison of amygdalar volume among the four groups

	Affected side (mm^3)	Unaffected side (mm^3)
AE (n=8)	1700.2±285.0	1189.1±227.4
Non-TLE (n=17)	1028.4±158.1	1093.2±174.3
MTLE+HS (n=15)	1060.8±150.9	1122.4±157.4
Normal (n=14)	**Larger side (mm^3)**	**Smaller side (mm^3)**
	1187.7±134.9	1105.5±117.6
	Left (mm^3)	**Right (mm^3)**
	1140.6±154.5	1152.6±108.4

Values are mean±SD.
Each of the four groups have been defined in the methods section.
Affected side means the AE side and seizure focus, and unaffected side means contralateral side of seizure focus.
Data for normal subjects are shown in two ways: the smaller versus larger sides and left versus right side. Smaller versus larger side in normal data is compared with unaffected versus affected sides in the patient groups, respectively. Left versus right side in normal is also compared with unaffected versus affected side as well as with affected versus unaffected side in the patient groups. Details are described in the results section.
AE, amygdalar enlargement; HS, hippocampal sclerosis; L, left; MTLE, mesial temporal lobe epilepsy; R, right.

Since we did not have direct recording from the amygdala by means of depth electrodes and as we did not have ictal SPECT, we could not definitively prove that the enlarged amygdala was epilpeptogenic. This needs further evaluation by means of more direct documentation such as invasive recording, if possible. As patients with AE and complex partial seizures are very rare in number, it might be difficult to obtain this in most institutes. We believe that it is worthwhile to extract and characterise this particular group of patients with AE and complex partial seizures among TLE patients, and this study could contribute in this regard. We need to pay attention not only to the degree of atrophy of the hippocampus but also to unilateral AE in TLE patients.

AE has not been fully recognised and documented from a surgical point of view because the hippocampus is typically considered to harbour epileptogenic foci rather than the amygdala. A pathological study of the amygdala in MTLE revealed neuronal loss and dendritic alterations.[21] With regard to the aetiologies of AE in the present study, there are several possibilities, such as neurodevelopmental abnormalities (ie, focal cortical dysplasia), very benign tumour (ie, hamartoma or low grade glioma)[22] or inflammatory process. Most of our patients developed symptoms in adulthood and there was no gadolinium enhancement by MRI and no significantly high signal changes in FLAIR images.

Recently, autoimmune processes in the development of partial epilepsies associated with anti-N-methyl-D-aspartate receptor antibody, anti-voltage gated potassium channel antibody, anti-glutamic acid decarboxylase antibody and other autoimmune antibodies have been raised as chronic epilepsies, and some of them reportedly showed a self-limited course.[23 24] As none of our patients showed increased regional glucose metabolism in the mesial temporal area, it is unlikely that a very active

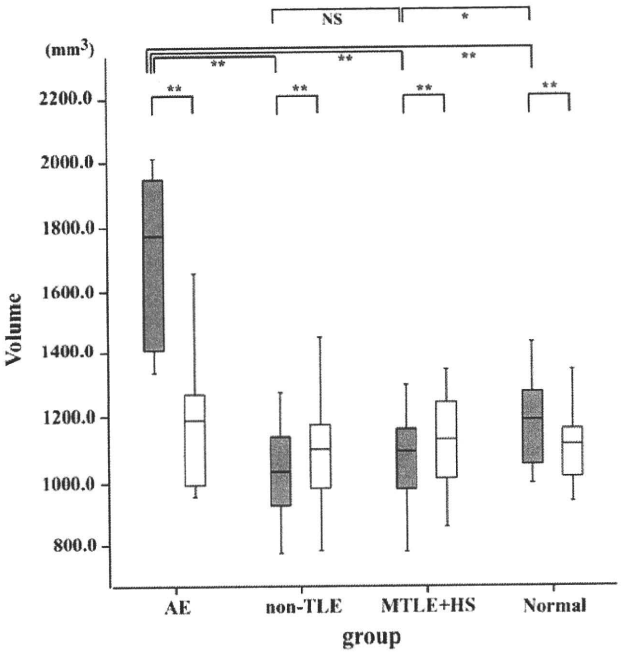

Figure 3 Comparison of amygdalar volumes in epilepsy patients (AE, non-TLE and MTLE+HS) and normal subjects (Normal). Closed boxes indicate the focus side volume in the patient groups and the larger side in normal subjects. Open boxes indicate the contralateral side to the epilepsy focus in the patient groups and the smaller side in normal subjects. The amygdalar volume is significantly larger on the ipsilateral side to the focus in AE ($p<0.01$) and it is the largest among the four groups. In non-TLE and MTLE+HS groups, the focus side shows the significantly smaller amygdalar volume, as opposed to the AE groups ($p<0.01$). The larger side volume in normal controls is also significantly smaller than the focus side in the AE group ($p<0.01$). *$p<0.05$, **$p<0.01$. Medians in each group appear as bars. AE, patients with amygdalar enlargement; non-TLE, patients with partial epilepsies other than temporal lobe epilepsy (TLE); MTLE+HS, patients with mesial TLE with hippocampal sclerosis.

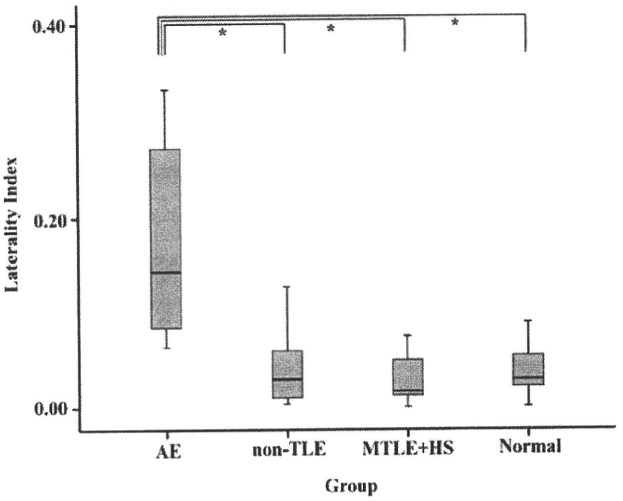

Figure 4 Comparison of laterality index (LI) in epilepsy patients (AE, non-TLE and MTLE+HS) and normal subjects (normal). LI is significantly larger in AE but not in the other three groups. Medians in each group appear as bars. AE, patients with amygdalar enlargement; non-TLE, patients with partial epilepsies other than temporal lobe epilepsy (TLE); MTLE+HS, patients with mesial TLE with hippocampal sclerosis.

inflammatory process was present at the time of investigation in our patients. However, the possibility that chronic, long lasting inflammatory processes with or without a self-limited course occurred could not be completely excluded.

Two patients (patient Nos 1 and 11) in our study underwent epilepsy surgery and showed non-specific gliosis and focal cortical dysplasia in the amygdala. Radiological and pathological findings were concordant, not showing features in the amygdala suggestive of tumour in patient Nos 1 and 11. Furthermore, repeated MRI examination in the five patients in the present study showed no increase in volume of the amygdala but no change in two and slight improvement in three. Therefore, these results suggest that AE patients in the present study could still be heterogenous in aetiology but being commonly benign in nature, as discussed above.

Overall clinical features of patients with AE

With regards to ictal semiology, three patients with AE in this study showed generalised tonic–clonic seizures without aura, similar to idiopathic generalised epilepsy. It seems distinct from typical MTLE, given that the amygdala might cause direct propagation to the thalamus through direct neuronal connections. Three other patients had ictal symptoms of anger and anxiety, which may be produced by direct amygdala activation. A previous study indicated that female patients with depression had significant AE on both sides.[25] However, only one patient (patient No 10) with bilateral AE and CPS in the present study was in a depressive state. Thus the main finding of this study could not be attributed to depression.

Only one patient (patient No 1) had intractable seizures and thus underwent surgery. Nine patients were free from seizures after antiepileptic drug administration, in particular after administration of a low dose of CBZ. Carbamazepine may have an effect on other antiepileptic drugs with higher concentrations, or CBZ itself may be effective against AE associated seizures, and thus further accumulation is needed. We should consider the presence of AE in TLE patients when they do not present with hippocampal sclerosis or atrophy. Future studies may reveal more patients who present with 'TLE and AE'.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (Approval No. 463).

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