＜シンポジウム 15―3＞最新のてんかんの病態と治療

てんかん研究の最前線

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Key words：広周波数帯域脳波，扁桃核腫大，辺縁系脳炎，常染色体優性外側側頭葉てんかん，遺伝子多型

てんかん発作とてんかんの診断では，病歴と症状（症候学），脳波（臨床神経生理学），画像検索（神経画像）の 3 基軸を中心に診断がなされ，短期的・長期的展望に基づいた治療がなされる．最近のてんかん研究の中で，以下に，上記の 3 基軸に関連する 1），2），3）と，てんかんの病態と治療に関連する遺伝子検索に関する 4），5）を概説する．

1）広域周波数帯域脳波（wide-band EEG analysis）の有用性[1)]

神経細胞の突発性脱分極変位（PDS）を反映する従来の脳波上の棘波・鋭波以外に，てんかん焦点の主に glia 細胞由来の発作時の緩徐な電位変化（直流変動から 0.1H 以下）と，てんかん焦点の神経細胞の population spike を反映する高周波変動（high frequency oscillation：HFO）（150～400Hz）は，てんかん原性をより特異的に反映する新たな指標として，とくに MRI 画像異常のない新皮質てんかんでの検討が期待されている（Imamura et al., 2011）（Fig. 1）．

2）側頭葉てんかん（TLE）における扁桃核腫大（amygdalar enlargement）の意義[2)]

海馬萎縮がなく MRI 上の信号変化はなくむしろ扁桃核体積が増加する TLE の一群が最近注目されている．海馬萎縮をともなう TLE に比較して，発症年齢が高く，熱性けいれんの既往がなく抗てんかん薬に対して発作は易治である．今後病態の検索が期待される（Mitsueda-Ono et al., 2011）（Fig. 2, 3）．

3）慢性てんかん症候群における神経系新規自己抗体の意義[3)]

抗 NMDA 受容体抗体による急性脳炎以外に，慢性の経過でてんかん症候群を鑑別が重要な病態が忠告されており，本抗体，抗 VGKC 抗体，抗 GAD 抗体などの関与が示唆されている．

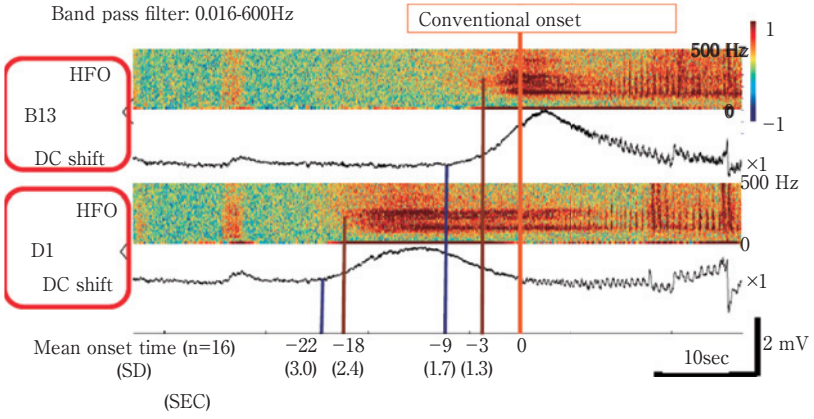

Fig. 1　A comparison between ictal DC shifts and HFO at subdural electrode B13 and D1, in a patient with right lateral temporal lobe epilepsy (Cited from Imamura et al., 2011). Before the conventional EEG onset (at time 0), both ictal DC shift and HFO occurred (by −22 sec and by −18 sec, respectively at Electrode D1) (by −9 sec and by −3 sec, respectively at Electrode B13) in recorded 16 seizures. Ictal DC shifts always preceded HFO in this particular patient (Cited from Imamura et al., 2011).

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4）チャンネル以外の遺伝子異常によるてんかん症候群[4)5)]

チャンネル異常と異なるLGI1（Leucin-rich glioma inactivated 1）がautosomal dominant layeral temporal lobe epilepsy（ADLTE）の原因遺伝子であることが解明され，phenotypeとphenotypeの関連，症状の家系内変動における修飾因子が検討されている（Kawamata et al., 2010）（Fig. 4，5）．

5）抗てんかん薬の代謝酵素の遺伝子多型と薬剤選択[6)]

clobazamがデスメチル体に代謝され両者ともに抗てんかん作用を示すが，後者の代謝酵素のCYP2C19の遺伝子多型により，投与量と効果，副作用の予測が可能となる．今後抗てんかん薬の治療計画に代謝酵素の遺伝子多型の検索は重要な情報を与える（安田ら，2009）．

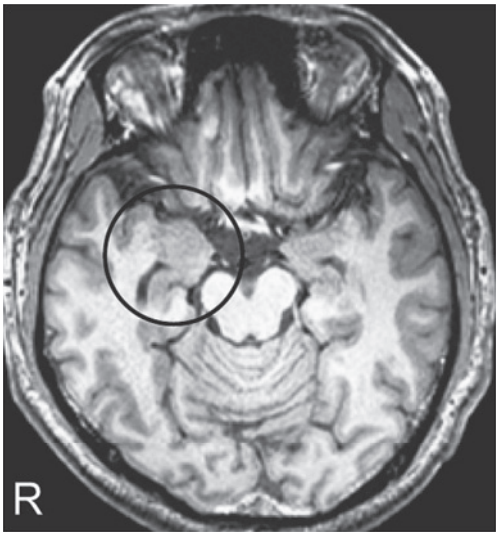

Fig. 2　A representative image of right amygdalar enlargement. The intensity of the amygdala does not show laterality (Cited from Mitsueda-Ono et al., 2011).

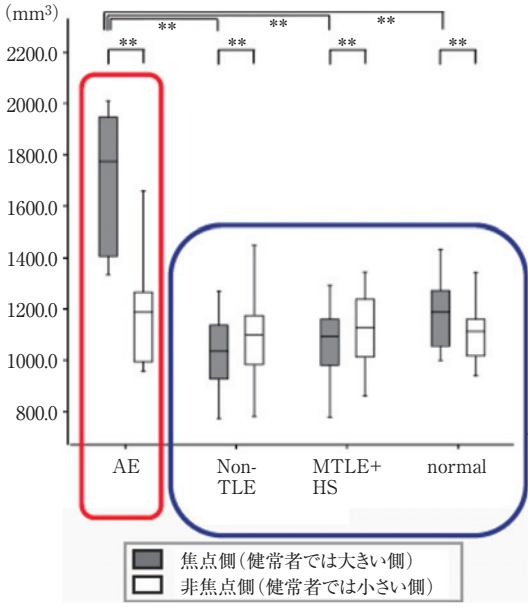

Fig. 3　A comparison of amygdalar volumes in epilepsy patients (AE, non-TLE and MTLE＋HS) and normal subjects (Normal).
Closed boxes indicate the focus side volume in the patient groups and the larger side in normal subjects. The amygdalar volume is significantly larger on the ipsilateral side to the focus 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 ($p<0.01$).
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 (Cited from Mitsueda-Ono et al., 2011).

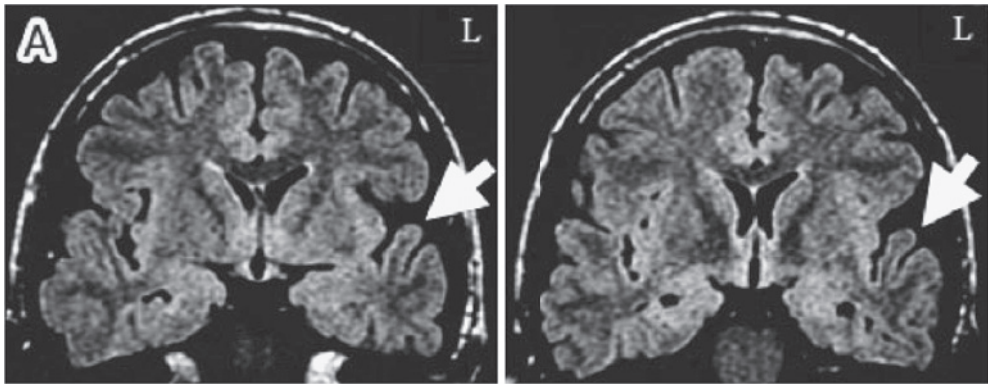

Fig. 4　A representative image of the left small superior temporal gyrus (arrowheads) in a patient with ADLTE (Cited from Fujita et al., 2009).

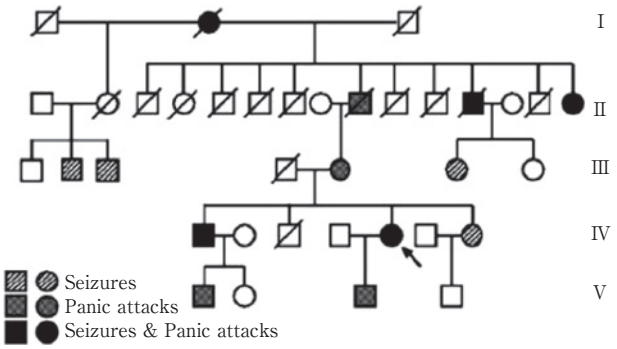

Fig. 5　Pedigree of a five-generation family with ADLTE. The proband case is indicated by the arrow. The clinical significance of this family is the diversity of the symptoms, for example, panic attack-like symptoms and seizures with auditory features. It seems that the affected phenotype of seizure skips generations (cited from Kawamata et al., 2010).

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Abstract

The leading edge of epilepsy research

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For diagnosis of seizure type and epilepsy syndrome, we always take all the three aspects of 1) history and symptoms (symptomatology), 2) EEG (clinical neurophysiology) and 3) neuroimaging into account, and thus an appropriate treatment approach based on both short- and long-term concerns is individualized.

Recent advances in clinical epileptology on the three aspects (i, ii, iii) and on genetic analysis (iv, v) are briefly introduced as follows.

i) Wide-band EEG analysis

Clinical EEG provides us with diagnostic information of epileptogenicity by epileptiform discharges, i.e., spikes, sharp waves, which reflects the paroxysmal depolarization shifts (PDS) in the epileptic neurons. Currently advanced technology has enabled us to record wide-band EEG: direct current (DC) shifts (Ikeda et al., 1996) and high frequency oscillation (HFO) (Bragin et al., 1999). The both conditions occurred together as early as electrodecremental pattern occurred or earlier than conventional ECoG changes, and that ictal DC shifts happened earlier than HFO on some occasions, that may suggest more active role of glia (Imamura et al., 2011).

ii) Amygdalar enlargement in patients with temporal lobe epilepsy (TLE).

With absence of hippocampal atrophy (HA), some patients with TLE clearly showed amygdalar enlargement on focus side; they had older onset age and better seizure control than HA. It may be a subtype of TLE (Mitsueda-Ono et al., 2011).

iii) Focal epilepsy syndrome as antibody-mediated gray matter disease?

Recently delineated antibodies to cell surface antigens such as anti-VGKC antibody, anti-GAD antibody or anti-NMDA receptor antibody could develop chronic epileptic condition, being apart from so-called acute limbic encephalitis with ovarian teratoma.

iv) Gentic abnormality in epilepsy other than channelopathy

Abnormality of LGI1 gene is responsible for autosomal dominant lateral temporal lobe epilepsy (ADLTE), where synaptic transmission could be impaired. Clinically significant divergence in symptoms and the degree of abnormality within family as well as between families remains to be solved (Kawamata et al., 2010).

v) Genetic polymorphism in CYP2C19 in drug choice

Information of genetic polymorphism in CYP2C19 could individualize drug choice and its dose in advance (Yasuda et al., 2009)

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Key words: wide-band EEG, amygdalar enlargement, limbic encephalitis, autosomal dominant lateral temporal lobe epilepsy (ADLTE), genetic polymorphism