実施される言語課題の項目が、記憶課題をかねる場合が多い。被験者には、あらかじめ、検査中の課題項目を覚えておくように指示しておく。記憶課題項目提示のタイミングは施設により異なる。麻酔による半身麻痺出現直後に課題を開始する施設や、麻酔薬注入後に最初の言語反応が認められてから記憶課題を実施する施設などがある。

記憶課題項目は、視覚的に提示する場合と聴覚的に提示する場合がある。視覚提示項目としては、日常的に使用する物品（時計、ペンなど）またはその線画、動植物の線画、文字言語（単語）、無意味図形、写真（人物、物品、動植物）などがある。聴覚提示項目としては、音声言語（単語、語句、簡単な文章など）が用いられる。提示項目数は施設ごとに異なるが、麻酔効果の持続する数分間に提示可能な項目数は最大十数個程度である。

一過性の半身麻痺と言語機能が回復したのを確認してから（通常、麻酔薬注入10～15分後）、記憶課題の再生、再認検査を実施する。自発的に再生できた項目に加えて、新規項目を含む複数項目から正しく再認できたものも正解として結果を評価する。

Wadaテストの記憶機能検査の主目的は、一側の側頭葉切除による術後障害として記憶障害を生じる危険がないかどうかを評価することである。患側の麻酔薬注入で記憶機能検査成績が67%（全記憶項目の3分の2）以上であれば、患側切除後に記憶障害の危険がなく、67%未満であれば術後記憶障害の危険がある、と判定する施設が多い[2]。カットオフを50%にしている施設もある。左右での差、およびてんかん焦点側との関係を考慮することも大切である。素材特異性記憶、すなわち、言語性記憶と非言語性記憶の術後記憶障害の危険性評価のためにWadaテストの記憶検査を用いる施設もあるが、結果にばらつきがあり、定説は得られていない。

2-2. 実施上の注意点

① リスク、合併症

Wadaテストは動脈穿刺、カテーテル挿入を伴う侵襲的検査である。脳血管造影検査と同等のリスクおよび不快感を患者に与えることに留意しなくてはならない。生じうる危険としては、動脈壁損傷、血栓による末梢または脳血管の塞栓、動脈スパズム、薬剤アレルギーなどがある。若年の被験者に比べて比較的高齢（平均51.3歳）の被験者で頚動脈解離の合併症が見られたとの報告もある[10]。多施設調査による合併症の発生率は、約1%である[6,7]。危険性については、十分に説明の上、文書による同意を得て実施する必要がある。

② 脳血管造影検査

脳血管造影検査は、血管の走行、異常の有無を確認すると同時に、Wadaテストの結果に影響を与える可能性のある血管走行の個人差、特に同側の後大脳動脈や対側の前大脳動脈への流入が無いかを確認するためにも必要である。脳血管撮影検査とWadaテストの実施順序は施設によって異なっており、脳血管撮影実施後にWadaテストを実施する場合や、一側のWadaテスト実施後に血管撮影検査を実施し、最後に対側のWadaテストを実施する場合がある。

③ 麻酔薬の種類

使用される麻酔薬は、上述のようにアモバルビタールが入手困難になったために、複数の代替薬が存在し、施設により使用薬は異なる。アモバルビタール以外に使用されている麻酔薬は、ペントバルビタール、メトヘキシタール、エトミダート、プロポフォール等がある（メトヘキシタールとエトミダートはわが国では未承認）。使用する麻酔薬によって、

使用量、麻酔からの回復時間が異なる。使用量は、注入半球の対側半身に一過性の麻痺を生じるのに十分な量で、施設ごとに使用量が定められている。なお、メトヘキシタールについては、アモバルビタールと比較して、検査中の発作が増えたとの報告もあり[11]、注意が必要である。

④ 脳波の同時記録

施設によっては、麻酔状態の評価のため脳波を測定しながらWadaテストを実施する。麻酔により同側半球に徐波が出現するのを確認して言語課題、記憶課題を実施し、徐波が消失してから記憶再生、再認検査を実施する。

⑤ 開始検査側の決定

ほとんどの施設で両側の検査を実施している。左右どちら側から検査を開始するかは、施設ごと、また症例ごとに異なる。患側から検査を開始する施設、想定される言語非優位側から検査を開始する施設がある。通常同日に両側の検査を実施するが、一側の検査を実施した後に、残存麻酔薬の影響を除外した上で、対側の検査を実施する必要がある。アモバルビタールを使用する場合、多くの施設では30分が麻酔薬の排出および効果消失に十分な時間と想定して検査を実施している。

（3）Wadaテストの有用性と留意点

Wadaテストが言語優位半球同定に関して、信頼性、妥当性の高い検査であることは論を待たないであろう。侵襲的検査であるために、複数回の検査で再現性を検討することは困難であるが、医療上の必要から再検査を実施した症例で、再現性を持って言語優位側が確認されたとの報告がある[12]。Wadaテストに代わる検査法について評価した研究も、言語優位側同定については、Wadaテストとの整合性をその検出感度の基準としている[13]。留意すべき点は、侵襲性の高い検査であることと、言語優位半球を同定する検査であり、個々の言語野の局在を同定するものではないということである。Broca野、Wernicke野等の言語野の同定には、皮質電気刺激検査、機能的MRI(fMRI)検査等を用いる必要がある。

D-3. 本研究におけるfMRIとWadaテストの比較

本研究では、fMRIで言語優位半球同定を行い、検査としての利点、欠点を検討し、Wadaテストの結果と比較することにより、今後の臨床利用方針について検討した。

検査は、11歳～49歳の年齢の被験者で実施した。若年者であっても言語課題を理解遂行でき、かつ静止可能であれば検査が可能であることを確認した。しかし、被験者が沈黙下で課題を行う必要があるため、検査結果は被験者が事前の指示通りに課題を実施できたかに左右される。発声に伴うアーチファクトで評価不能であった被験者は33歳であり、年齢よりも、被験者の理解レベル、課題遂行能力の検査前評価が必須であることが明らかになった。

薬剤アレルギーのためWadaテストが中止となった症例では、fMRIによる言語優位側判定が可能であった。このことから、合併症等でWadaテスト実施不能の症例ではfMRIによる言語優位側同定を代替検査として使用することができることを確認した。

fMRIの結果とWadaテストの結果が一致しなかった症例のうち、1例は、皮質形成異常があり、1例は、一側半球の著明な萎縮があった。原因のひとつには、fMRIによる賦活部位判定で統計解析の手法を用いるために被験者の脳画像を標準化したことがあると考えられる。広範囲の脳萎縮や病変のある症例では、fMRIの結果は慎重に評価する必要が

あることが明らかになった。

E. 結論

Wadaテストに代わる非侵襲的検査法は、複数あるが、それぞれに利点、留意点がある。fMRIは、最も有望な検査法であるが、臨床的な普及のためには、使用する言語・記憶検査課題を含め、検査技術の向上と標準化が望まれる。機器としてはfMRI臨床的に普及しているものであり、また、高解像度の脳画像検査が可能である。しかしながら、以下のような制限がある。1）機器はfMRI撮像可能な機種、性能を備えている必要がある。2）動きのアーチファクトに弱く、一定時間静止できない被験者は検査不能。3）ペースメーカーや、頭頸部に金属装置のある被験者は検査不能。4）大きな脳内病変や血管奇形は、脳機能局在の評価が不正確になる可能性がある。5）撮影用コイル、検査台の大きさの関係で、頭が大きい被験者や極度の肥満者は検査できない。6）表出言語を伴う検査課題は頭顎部の動きでアーチファクトが生じて使用できない。7）課題は全て被験者の沈黙下で行うため被験者が十分に検査に協力し課題遂行を行うこと前提とする。

反復性経頭蓋磁気刺激法（rTMS）は、コイルに強力な電流を流して電磁誘導による垂直方向の磁場を発生させ、その磁場の周囲に生じる二次電流により脳神経細胞を刺激する。rTMSは、特定の脳部位に一過性の機能障害を生じさせることによって機能評価をするという点で、Wadaテストと共通点があるが、刺激による痛みや頭痛が生じることがあり、また、てんかん症例の場合には、発作誘発の危険性があるため、Wadaテストの代替法としての研究報告は少ない。

MEGは、神経細胞の活動によって生じる微弱な磁場を計測する方法で、非侵襲的な検査であるが、臨床的に普及した検査機器ではなく、また、複雑な検査結果解析を要する。

近赤外線分光法（NIRS）を用いた光トポグラフィは、神経細胞の活動に伴う血液動態を検出する間接的検査法である。安全に実施でき、また、被験者の体動の影響を比較的受けにくい検査法ではあるが、観察できるのは、頭皮から20mmまでの脳表層の活動のみである。

SPECTとPETも神経細胞の活動に伴う血液動態を検出する間接的検査法である。放射性同位元素を用いるため、被爆の影響を考慮する必要がある。

Wadaテストは、言語優位側同定に関して最も信頼度の高い検査である。しかしながら、侵襲を伴う検査であるために、被験者の負担が大きく、また、合併症の危険も伴う。そのため、適用については、対象となる症例ごとに慎重に危険性と有益性を検討して判断する必要がある。

本研究において実施した検査では、83.3%の症例で、fMRIとWadaテストで一致する結果が得られた。しかしながら、正確な検査結果を得るためには、検査中の課題遂行に対する被験者の十分な理解と協力が必須である。また、被験者の課題遂行が十分であっても、脳内病変の大きさ、性質により、結果の信頼性が低下する可能性がある。今後は、術前言語優位側を同定する手法、ならびに術後記憶障害発生予測のための検査手法としての位置づけを検討し、臨床的に有効な使用法の検証を目指す予定である。

参考文献

1) Wada J. A new method for the determination of the side of cerebral speech dominance: a preliminary report on the intracarotid injection of Amytal in man. 医学生物学. 14:221-222, 1949.

2) Dinner DS, Loddenkemper T. Wada test and epileptogenic zone. In Lüders HO ed. Textbook of Epilepsy Surgery. Informa UK, London. 2008. pp844-857.
3) 亀山茂樹、増田浩、村上博淳ほか。てんかん患者における言語機能再編と記憶 - ワダテストからの知見 - 。てんかん研究。25: 406-413, 2008.
4) Engel Jr J, Rausch R, Lieb JP, et al. Correlation of criteria used for localizing epileptic foci in patients considered for surgical therapy of epilepsy. Ann Neurol 9:2114-2124, 1981
5) Loring DW, Meador KJ, Lee GP, et al. Wada memory performance predicts seizure outcome following anterior temporal lobectomy. Neurology, 44:2322-2324, 1994
6) Rausch R. Intraarterial amobarbital procedures. In: Engel Jr J. ed. Surgical treatment of the epilepsies. Raven Press. New York. 1993. pp341-357.
7) Haag A, Knake S, Hamer HM, et al. The Wada test in Austrian, Dutch, German, and Swiss epilepsy centers from 2000 to 2005: a review of 1421 procedures. Epilepsy Behav. 13(1):83-89. 2008
8) Baxendale S, Thompson PJ, Duncan JS. The role of the Wada test in the surgical treatment of temporal lobe epilepsy: an international survey. Epilepsia, 49(4): 715-720, 2008
9) Benbadis SR, Dinner DS, Chelune GJ, et al. Objective criteria of reporting language dominance by intracarotid amobarbital procedure. J Clin Exp neuropsychol 1995:682-690, 1995.
10) Loddenkemper T, Morris HH 3rd, Perl J 2nd Carotid artery dissection after the intracarotid amobarbital test. Neurology, 59(11):1797-1798, 2002
11) Loddenkemper T, Möddel G, Schuele SU, et al. Seizures during intracarotid methohexital and amobarbital testing. Epilepsy Behav. 10(1):49-54, 2007
12) Loddenkemper T, Morris HH, Lineweaver T, et al. Repeated intracarotid amobarbital tests. Epilepsia, 48:553-558. 2007.
13) Abou-Khalil B. methods for determination of language dominance: The Wada test and proposed noninvasive alternatives. Curr Neurol Neurosci Rep, 7:483-490, 2007

G. 研究発表

1. 論文

1. Sato W, Kochiyama T, Uono S, Matsuda K, Usui K, Inoue Y, Toichi M. Rapid amygdala gamma oscillations in response to fearful facial expressions. Neuropsychologia. 2011;49(4):612-7.
2. Wrench JM, Matsumoto R, Inoue Y, Wilson SJ. Current challenges in the practice of epilepsy surgery. Epilepsy & Behavior 2011;22:23-31.
3. 小出泰道、長尾雅悦、福島克之、宇留野勝久、笹川睦男、高橋幸利、岡田久、渡邉宏雄、星田徹、井上美智子、後藤一也、馬場啓至、石津棟暎、井上有史。トピラマートの有効性と安全性についての多施設共同研究。てんかん研究 2011;29:3-13.
4. 大谷英之、田中正樹、笹川睦男、溝渕雅弘、井上有史。抗てんかん薬と

妊娠に関するヨーロッパを中心とした国際共同研究 (EURAP) における日本国内登録症例の検討（第1報)。てんかん研究 2011;29:28-35.
5. Usui N, Terada K, Baba K, Matsuda K, Nakamura F, Usui K, Yamaguchi M, Tottori T, Umeoka S, Fujitani S, Kondo A, Mihara M, Inoue Y. Clinical significance of ictal high frequency oscillations in medial temporal lobe epilepsy. Clinical Neurophysiology 2011; 122: 1693–1700
6. Yamazaki E, Takahashi Y, Akasaka N, Fujiwara T, Inoue Y. Temporal changes in brain MRI findings in Rasmussen syndrome. Epileptic Disord. 2011;13(3):229-239.
7. Ikeda H, Imai K, Ikeda H, Shigematsu H, Shishido T, Takayama R, Fujiwara T, Takahashi Y, Inoue Y. Lamotrigine is favorable for startle-induced seizures. Epileptic Disord. 2011;13(3):277-283.
8. Usui N, Mihara T, Baba K, Matsuda K, Tottori T, Umeoka S, Kondo A, Nakamura F, Terada K, Usui K, Inoue Y. Versive seizures in occipital lobe epilepsy: Lateralizing value and pathophysiology. Epilepsy Res. 2011;97(1-2):157-61 PubMed PMID: 21885252.
9. Terada K, Umeoka S, Usui N, Baba K, Usui K, Fujitani S, Matsuda K, Tottori T, Nakamura F, Inoue Y. Uneven interhemispheric connections between left and right primary sensori-motor areas. Hum Brain Mapp 2012;33:14-26.
10. Sato W, Kochiyama T, Uono S, Matsuda K, Usui K, Inoue Y, Toichi M. (2011) Rapid Amygdala Gamma Oscillations in Response to Eye Gaze. PLoS ONE 6(11): e28188. doi:10.1371/journal.pone.0028188
11. 木村記子、井上有史、岡田俊。てんかんに併存する強迫性・衝動性とてんかん治療の影響。臨床精神医学 2011:14;615-621.
12. 井上有史。てんかんにおける医療連携。精神医学 2011;53: 461-7.
13. 宍戸丈郎、井上有史。てんかん薬物治療ガイドライン。綜合臨床 2011;60(4):601-2.
14. 山崎悦子、井上有史。成人てんかんの薬物治療。Modern Physician 2012;32(3):319-22
15. 山本吉章、井上有史。抗てんかん薬。医薬ジャーナル、新薬展望 2012、2012;48(S-1):282-6
16. 清水秀明、井上有史。特発性全般てんかん。臨床精神医学 2011;40 増刊号 :400-402
17. 井上有史。てんかん。山内俊雄、小島卓也、倉知正佳、鹿島晴雄編。専門医をめざす人の精神医学第3版。医学書院 , 2011:356-364
18. 井上有史。てんかん。こころとからだの救急患者対応、日本こころとからだの救急学会編著、MC メディカ出版、2011:73-82.
19. 井上有史。「けいれん」で搬送されてきた患者。こころとからだの救急患者対応、日本こころとからだの救急学会編著、MC メディカ出版、2011:139-144.
20. 井上有史他。MOSES ワークブック：トレーナー教本。MOSES 企画委員会、クリエイツかもがわ、2011

2．学会・研究会等における発表

Inoue Y. The possibility of surgical treatment of partial epilepsy associated with genetic abnormalities. Parallel session, Genetic partial epilepsies: the clinical, genetic and the therapeutic spectrum. 29th International Epilepsy Congress, Roma, 29 Aug - 1 Sep, 2011.

3．学会等における講演

1. Inoue Y. Medical intractability, surgical indication & timing. Workshop on epilepsy surgery: evaluation, surgical procedures and outcomes, Guilin, China 2011.4.8-9
2. Inoue Y. Seizure semiology. Workshop on epilepsy surgery: evaluation, surgical procedures and outcomes, Guilin, China 2011.4.8-9
3. Inoue Y. Neuropsychology/psychiatry. Workshop on epilepsy surgery: evaluation, surgical procedures and outcomes, Guilin, China 2011.4.8-9
4. Inoue Y. Surgery outcome. Workshop on epilepsy surgery: evaluation, surgical procedures and outcomes, Guilin, China 2011.4.8-9
5. Nishida T, Inoue Y. Postictal psychiatric manifestations. Symposium: Psychiatric aspects of epilepsy, World Psychiatric association Regional Meeting, Kaohsiung, Taiwan, Nov. 4, 2011.
6. 井上有史。内側側頭葉てんかんをめぐって。第８回御茶ノ水てんかんカンファレンス、2011.5.13、東京
7. 井上有史。静岡てんかんセミナー、2011.9.9、静岡
8. 井上有史。発作症状を読み解く。第30回秋田県てんかん研究会、秋田市、2011.10.21
9. 井上有史。内側側頭葉てんかんをめぐって。第19回てんかん機能外科懇話会特別講演、大阪、2012.2.10
10. 井上有史。てんかんのケアについて。Epilepsy Forum in Gifu 2012、岐阜、2012.3.3
11. 井上有史。てんかんと記憶障害。京都大学精神科セミナー、京都、2012.1.18

H. 知的財産権の出願・登録状況

1. 特許取得
   なし
2. 実用新案登録
   なし
3. その他
   なし

III　研究成果の刊行に関する一覧表

厚生労働科学研究費補助金研究報告書

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
井上有史	てんかん	山内俊雄、小島卓也、倉知正佳、鹿島晴雄	専門医を目指す人の精神医学	医学書院	東京	2011	356-364
井上有史	てんかん	日本心とからだの救急学会	心とからだの救急患者対応	ＭＣメディカ	大阪	2011	73-82
井上有史	「けいれん」で搬送されてきた患者	日本心とからだの救急学会	心とからだの救急患者対応	ＭＣメディカ	大阪	2011	139-144
井上有史	MOSESワークブック：トレーナー教本	MOSES企画委員会	MOSESワークブック：トレーナー教本	クリエイツかもがわ	京都	2011	1-180
井上有史	災害に備えて	井上有史、池田仁	新てんかんテキスト	南江堂	東京	2012	155-156
馬場好一	外科治療の方法	井上有史、池田仁	新てんかんテキスト	南江堂	東京	2012	95-97
寺田清人	脳波検査	井上有史、池田仁	新てんかんテキスト	南江堂	東京	2012	38-40
寺田清人	てんかん	泉孝英	ガイドライン外来診療2011-今日の治療のために	日系メディカル開発	東京	2011	482-485
寺田清人、井上有史	抗てんかん薬	高久史麿	治療薬ハンドブック2011	じほう	東京	2011	43-68
寺田清人、井上有史	抗てんかん薬	高久史麿	治療薬ハンドブック2012	じほう	東京	2012	44-69
臼井桂子	てんかんと高次脳機能	井上有史、池田仁	新てんかんテキスト	南江堂	東京	2012	53-54
臼井桂子	てんかんと性格・行動	井上有史、池田仁	新てんかんテキスト	南江堂	東京	2012	57-58

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Sato W, Kochiyama T, Uono S, Matsuda K, Usui K, Inoue Y, Toichi M	Rapid amygdala gamma oscillations in response to fearful facial expressions	Neuropsychologia	49(4)	612-617	2011
Wrench JM, Matsumoto R, Inoue Y, Wilson SJ	Current challenges in the practice of epilepsy surgery	Epilepsy Beh	22	23-31	2011
Usui N, Terada K, Baba K, Matsuda K, Nakamura F, Usui K, Yamaguchi M, Tottori T, Umeoka S, Fujitani S, Kondo A, Mihara M, Inoue Y	Clinical significance of ictal high frequency oscillations in medial temporal lobe epilepsy	Clin Neurophysiol	122	1693-1700	2011
Yamazaki E, Takahashi Y, Akasaka N, Fujiwara T, Inoue Y	Temporal changes in brain MRI findings in Rasmussen syndrome	Epileptic Disord	13	229-239	2011
Ren L, Terada K, Baba K, Usui N, Umeoka S, Usui K, Matsuda K, Tottori T, Nakamura F, Mihara T, Inoue Y	Ictal very low frequency oscillation in human epilepsy patients	Ann Neurol	69	201-206	2011
Ikeda H, Imai K, Ikeda H, Shigematsu H, Shishido T, Takayama R, Fujiwara T, Takahashi Y, Inoue Y	Lamotrigine is favorable for startle-induced seizures	Epileptic Disord	13	277-283	2011
Usui N, Mihara T, Baba K, Matsuda K, Tottori T, Umeoka S, Kondo A, Nakamura F, Terada K, Usui K, Inoue Y	Versive seizures in occipital lobe epilepsy: Lateralizing value and pathophysiology	Epilepsy Res	97	157-161	2011
Terada K, Umeoka S, Usui N, Baba K, Usui K, Fujitani S, Matsuda K, Tottori T, Nakamura F, Inoue Y	Uneven interhemispheric connections between left and right primary sensori-motor areas	Hum Brain Mapp	33	14-26	2012

Sato W, Kochiyama T, Uono S, Matsuda K, Usui K, Inoue Y, Toichi M	Rapid amygdala gamma oscillations in response to eye gaze	PLoS One	6	e28188	2011
Hitomi T, Ikeda A, Kondo T, Imamura H, Inouchi M, Matsumoto R, Terada K, Kanda M, Matsuhashi M, Nagamine T, Shibasaki H, Takahashi R	Increased cortical hyperexcitability and exaggerated myoclonus with aging in benign adult familial myoclonus epilepsy	Movement Disord	26	1509-1514	2011
Sato W, Kochiyama T, Uono S, Matsuda K, Usui K, Inoue Y, Toichi M	Temporal Profile of Amygdala Gamma Oscillations in Response to Faces	J Cogn Neurosci	Epub ahead of print		2011
臼井桂子、寺田清人、井上有史	Wadaテストによる言語・記憶機能検査-てんかん外科の手術前検査における役割-	Epilepsy	15	117-123	2011
小出泰道、長尾雅悦、福島克之、宇留野勝久、笹川睦男、高橋幸利、岡田久、渡邉宏雄、星田徹、井上美智子、後藤一也、馬場啓至、石津棟暎、井上有史	トピラマートの有効性と安全性についての多施設共同研究	てんかん研究	29	3-13	2011
大谷英之、田中正樹、笹川睦男、溝渕雅弘、井上有史	抗てんかん薬と妊娠に関するヨーロッパを中心とした国際共同研究(EURAP)における日本国内登録症例の検討（第１報）	てんかん研究	29	28-35	2011
木村記子、井上有史、岡田俊	てんかんに併存する強迫性・衝動性とてんかん治療の影響	臨床精神医学	14	615-621	2011
馬場好一、臼井直敬、寺田清人、臼井桂子、松田一己、鳥取孝安、井上有史、三原忠紘	内側側頭葉てんかんの頭蓋内脳波における発作時高周波成分の臨床的意義に関する研究	(財)てんかん治療研究振興財団研究年報	22		2011
井上有史	てんかんにおける医療連携	精神医学	53	461-467	2011
宍戸丈郎、井上有史	てんかん薬物治療ガイドライン	綜合臨床	60	601-602	2011
山崎悦子、井上有史	成人てんかんの薬物治療	Modern Physician	32	319-322	2012
山本吉章、井上有史	抗てんかん薬	医薬ジャーナル、新薬展望2012	48(S-1)	282-286	2012

清水秀明、井上有史	特発性全般てんかん	臨床精神医学	40増刊号	400-402	2011

IV　研究成果の刊行物・別刷

Clinical Neurophysiology 122 (2011) 1693–1700

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Clinical significance of ictal high frequency oscillations in medial temporal lobe epilepsy

Naotaka Usui *, Kiyohito Terada, Koichi Baba, Kazumi Matsuda, Fumihiro Nakamura, Keiko Usui, Miyako Yamaguchi, Takayasu Tottori, Shuichi Umeoka, Shigeru Fujitani, Akihiko Kondo, Tadahiro Mihara, Yushi Inoue

National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan

ARTICLE INFO

Article history:
Accepted 7 February 2011
Available online 12 March 2011

Keywords:
High frequency oscillations
Medial temporal lobe epilepsy
Intracranial EEG
Fast ripples
Epilepsy surgery

HIGHLIGHTS

- Ictal high frequency oscillations (HFO) were detected unilaterally.
- They were detected ipsilateral to the side of hippocampal sclerosis (HS).
- They were not propagated contralaterally except for one patient.
- In one case with bitemporal onset, ictal HFO were detected only on the side of HS.
- Ictal HFO in the medial temporal lobe is the electrophysiological signature of HS.

ABSTRACT

Objective: To clarify the clinical significance of ictal high frequency oscillations (HFO) in the medial temporal lobe.
Methods: This study included 19 patients who underwent intracranial electrode implantation in bilateral temporal lobes and had at least one seizure recorded at 1 kHz sampling rate. The characteristics of ictal HFO in the medial temporal lobe, and the relations between the presence of HFO, pathology, and postoperative seizure outcome were analyzed.
Results: Ictal HFO were detected from medial temporal structures in 11 patients with medial temporal lobe epilepsy (MTLE). Among eight patients without HFO, only three were diagnosed with MTLE. Ictal HFO were detected from unilateral medial temporal structures ipsilateral to the side of hippocampal sclerosis (HS). In one patient with bitemporal independent seizure onset, ictal HFO were detected only on the side of HS. HS was detected in all 11 patients with HFO, but in only one of four patients without HFO. Seizure outcome did not differ between patients with and without HFO.
Conclusions: Ictal HFO in the medial temporal lobe may be a specific marker for MTLE with HS.
Significance: Recording of ictal HFO in the medial temporal lobe may be useful for presurgical evaluation of MTLE.

1. Introduction

Electrophysiological studies in animals revealed that high frequency oscillations (HFO) with frequencies of 400–1000 Hz were recorded in the vicinity of epileptogenic foci (Gastaut and Fischer-Williams, 1959). Recently, HFO have attracted attention in epilepsy surgery. Previous studies have reported the characteristics of HFO in medial temporal lobe epilepsy (MTLE) as follows; (1) recorded from hippocampus or entorhinal cortex; (2) frequencies ranging from 170 to 400 Hz, usually with fast frequencies of 260–270 Hz [fast ripple: FR (Bragin et al., 1999), very high frequency band: VHF (Jirsch et al., 2006)]; (3) usually detected on the side of surgical resection; (4) not detected in the region of secondary propagation; (5) can be recorded ictally or interictally; (6) appear as clusters of short bursts with a duration of 6–53 ms; (7) usually associated with ictal spikes on conventional EEG; (8) detected by only 1–2 macroelectrode channels; and (9) low amplitudes of 5–30 μV (Bragin et al.,1999, 2002; Jirsch et al., 2006; Yamaguchi et al., 2008).

As for ictal HFO, Jirsch et al. (2006) reported ictal HFO in 10 patients with focal seizures, including four with medial temporal onset seizures. They used the EEG seizure onset as a surrogate for the epileptogenic area, and did not evaluate the postoperative seizure

* Corresponding author. Address: National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Urushiyama 886, Aoi-ku, Shizuoka 420-8688, Japan. Tel.: +81 54 245 5446; fax: +81 54 247 9781.
E-mail address: n-usui@szec.hosp.go.jp (N. Usui).

1388-2457/$36.00 © 2011 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.clinph.2011.02.006

Table 1
Clinical characteristics of 19 patients.

Patient	Age (yrs)/sex	Age at onset (yrs)	Semiology	Interictal EEG	Ictal EEG
1	20/M	7	Automotor	Lt	Rt
2	21/F	1	Automotor	Bil (Lt predominant)	Rt
3	32/F	10	Dysmnestic aura → automotor	Rt	Rt
4	36/F	15	Aura → automotor	Rt	Lt
5	43/F	9	Dialeptic	Bil (Lt predominant)	Lt
6	34/F	1	Aura → automotor	Bil (Lt predominant)	Bil (Lt predominant)
7	30/F	4	Automotor	Rt	Lt
8	19/M	3	Abdominalaura → automotor	Bil (Lt predominant)	Bil (Rt predominant)
9	43/F	9	Aura → dialeptic	Rt	Lt
10	37/F	18	Automotor	Bil	Lt
11	39/M	10	Aura → automotor	Bil (Rt predominant)	Rt
12	36/M	27	Dialeptic	Bil	Lt
13	21/M	15	Abdominal aura → dialeptic	Rt	Rt
14	29/M	16	Aura → automotor	Bil	Lt
15	26/F	15	Automotor	Rt	Rt
16	26/M	5	Hypermotor	Bil	Bil
17	16/F	11	Automotor	Bil	Bil (Lt predominant)
18	31/F	11	Automotor	Lt	Bil (Lt predominant)
19	21/M	15	Aura → automotor	Bil	Lt

M: male; F: female; Rt: right; Lt: left; Bil: bilateral independent spikes on right and left.

outcome. Khosravani et al. (2009) also studied ictal HFO in seven TLE patients. However, the clinical significance of ictal HFO on surgical decision-making has not been fully examined.

To clarify the clinical relevance of ictal HFO, we analyzed their characteristics including the spatial distribution of ictal HFO in the medial temporal lobe, and compared the presence or absence of ictal HFO with hippocampal pathology and postoperative seizure outcome. We also demonstrated the clinical usefulness of detecting ictal HFO in surgical decision-making for bitemporal epilepsy.

2. Patients and methods

2.1. Patients

Previously, we proposed the following criteria for omitting intracranial EEG monitoring in patients with temporal lobe epilepsy; (1) appearance of focal epileptic discharges in unilateral sphenoidal lead during the phase of simple partial seizures, or unilateral discharges predominantly in the sphenoidal lead during the early phase of complex partial seizures; (2) interictal spikes on scalp-recorded EEGs localizing unilaterally in the anterior region of the temporal lobe, and if bilaterally independent, presenting with unilateral predominance in a ratio of greater than 4:1; (3) presence of autonomic signs in the initial phase of signal symptoms; and (4) neuroimaging findings in the mesial temporal region showing elongated T2 on MRI and HS, or a tumorous lesion (Mihara et al., 1992). Consequently, between May 2005 and May 2008, 19 patients underwent implantation of combined depth and subdural electrodes in bilateral temporal lobes (Mihara and Baba, 2001), and had at least one seizure recorded at 1 kHz sampling rate. These 19 patients were included in this study. Before intracranial video/EEG monitoring, all patients underwent noninvasive presurgical evaluations including history-taking, video/scalp sphenoidal EEG monitoring, neuroimagings, and neuropsychological tests. Brain MRI was performed at 1.5 tesla and 5-mm slice thickness, and axial, coronal, and sagittal T1-weighted, T2-weighted, and FLAIR images were acquired. The clinical characteristics of the 19 patients are shown in Table 1. Seizures were classified by the semiological seizure classification proposed by Lüders et al. (1998).

Depth electrodes (Unique Medical, Japan, 0.8 mm diameter, 1 mm length, either 5 or 10 mm center-to-center spacing) were placed in bilateral hippocampi and amygdala using MRI stereotaxy. Subdural electrodes (Ad-tech Medical Instrument, Racine, WI. 2.3 mm contact, effective area 4.15 mm^2, 10 mm spacing) were also placed over bilateral temporal regions including the basal and anterior aspects, and the adjacent parieto-occipital areas (Fig. 1). Reference electrodes were placed on the surface of the skull, with the contacts of the electrodes facing away from the skull to avoid the referential activation. Analyses were performed on referential montages. Antiepileptic medications were reduced, and EEG recording was started approximately 1 week after electrode placement and continued for approximately 2 weeks. The EEG signals were digitally recorded by EEG-1000 (Nihon Kohden) at a sampling rate of 200 Hz and a time constant of 10 s for conventional EEG analysis. For detection of HFO, EEG was low pass filtered at 300 Hz, recorded at a sampling rate of 1 kHz and a time constant of 10 s.

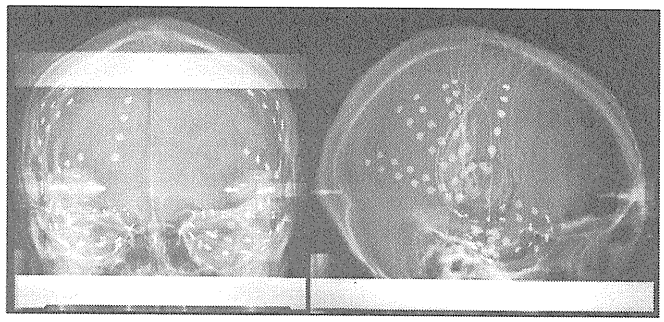

Fig. 1. Skull X ray showing the location of intracranial electrodes. Left: anteroposterior view. Right: lateral view. Two depth electrodes are inserted into the medial temporal structure on each side. RA and LA are aimed at amygdala, and RH and LH are at hippocampus. Basal temporal areas are covered by subdural electrodes.

Before the electrodes were removed, MRI was performed to confirm the locations of the electrodes. MRI findings confirmed that in all patients, the amygdalar depth electrodes were placed correctly, and the hippocampal depth electrodes were placed in the subiculum or Ammon's horn.

After completing the invasive monitoring, 13 patients underwent amygdalohippocampectomy, three anterior temporal lobectomy, including medial temporal structures, and one lateral temporal resection sparing the medial temporal structures. The remaining two patients did not undergo resective surgery. Postoperative follow-up ranged from 12 to 54 months.

2.2. Visual inspection of ictal HFO

The ictal EEGs were analyzed visually for the presence of distinct oscillations with frequencies of 200 Hz and higher (fast ripples) by two clinical epileptologists (N.U. and K.T.). Both observers jointly reviewed the data and established a consensus. High frequency activities slower than 200 Hz (ripples) were not analyzed in the current study. To visualize high frequency activities, the horizontal (time) and vertical (amplitude) axes of the EEG display were expanded, and the signals were digitally high-pass filtered at 50 Hz (time constant of 0.003 s). HFO were defined as follows: (1) appearing on several occasions at a similar frequency in the same channel; (2) visually detectable as sinusoidal waves, and (3) containing at least four consecutive peaks with similar inter-peak intervals. Typical examples of ictal HFO are shown in Figs. 2–4. The frequencies, amplitudes, locations, durations and intervals of HFO were measured on the CRT screen. Moreover, total durations of HFO events, as well as the intervals between HFO onset and EEG onset on conventional EEG, were also measured. Seizure onset on conventional EEG was defined as localized, sustained, rhythmic, or spiking EEG pattern with a frequency >2 Hz, visually distinguished from background activity (Spencer et al., 1992). Ictal EEG was reviewed 5 min before EEG onset defined by conventional EEG. Interictal EEG of 5 min was also reviewed in each patient. The state (awake or asleep) of the patients during interictal recording was variable. In 15 patients, the interictal data were more than 2 h away from the seizures. However, the interictal data were within 2 h (30 min away from seizures in one patient, 40 min in two, and 1 h and 40 min in one) from seizures in the remaining four patients. In patients who had interictal HFO, the onset of ictal HFO were defined as the time at which HFO appeared regularly and the interval of HFO became shorter than 3 s. In patients who had interictal HFO with a mean interval of less than 3 s, the onset of ictal HFO were defined as the time at which the mean interval of HFO became shorter than 1 s.

2.3. Correlation with hippocampal pathology and seizure outcome

In 16 patients who underwent medial temporal resection, the degree of hippocampal neuron loss in the resected specimens was evaluated. Hippocampal pathology was classified using Blümcke's classification (Blümcke et al., 2007) as follows: no MTS: normal hippocampus, MTS type 1a: classic hippocampal sclerosis with severe cell loss in CA1and moderate loss in remaining sectors, MTS type 1b: severe hippocampal sclerosis affecting all hippocampal sectors, MTS type 2: severe cell loss in CA1 and only mild pathology within remaining sectors (i.e. CA1-sclerosis), MTS type 3: end folium sclerosis with moderate cell loss in all sectors with exception of CA1.

Seizure outcomes were evaluated using Engel's criteria. The relations between the presence of ictal HFO, pathology of resected hippocampi, and postoperative seizure outcome were analyzed statistically by using Fisher's exact probability test. An error probability of less than 0.05 was considered to be indicative of significance.

Table 2
Detection and parameters of ictal high frequency oscillations in 19 patients.

Patient	Seizure onset zone	Number of seizures	Electrodes detecting HFO	Frequency (Hz)	Amplitude (μV)	Duration (ms)	Inter-HFO Interval (s)	Total duration (s)	Time lag to EEG onset (s)
1	Lt MT (LA1-2, LH1-3, LBA1-2, LBP1-2)	3	LH1-3	200–250	25.4 (20.0–33.6)	75 (65–93)	1.15 (0.96–1.30)	30.3 (15–43)	23.2 (14–38)
2	Bil MT (RA1, RH1–2, RBP1-2, LA1-6, LH1-5, LBA1-6, LBP1-5)	3 (Rt onset)	RA1,RH1-2, RBP1	200–333	42.7 (17.8–73.2)	42 (32–61)	1.65 (1.50–1.96)	61.7 (26–91)	30.5 (8–53)
		2 (Lt onset)	RA1,RH1-2, RBP1	200–333	39.4 (18.3–71.9)	40 (35–44)	0.70 (0.60–0.80)	79.5 (70–89)	74.5 (65–84)
3	Lt MT (LBA1, LBP1)	1	LH1-3	250–333	28.7 (12.5–44.7)	27.4 (23–38)	0.37 (0.25–0.64)	71	28
4	Rt MT (RA1-2, RH1-2, RBA1-3, RBP1-3)	11	RA1	200–333	35.3 (7.4–38.2)	19 (13–37)	0.82 (0.26–1.59)	28.8 (13–63)	20 (7–27)
5	Lt MT (LA1-2, LH1-3, LBP1-2)	2	LA1-2, LBP2	200–333	27.4 (14.7–44.5)	26 (24–28)	0.60 (0.56–0.65)	41.0 (30–52)	45.0 (38–52)
6	Lt MT (LA1-2, LH1-3, LBP1-2)	3	LH2-3, LBP1	200–333	22.8 (13.5–27.1)	32 (30–33)	1.11 (0.48–1.92)	45.0 (17–75)	33.7 (24–44)
7	Rt MT (RA1-2, RH1-2)	3	RA1-2, RH1-2, LA1-2, LH1	200–333	21.6 (11.6–35.0)	27 (27–28)	1.13 (1.10–1.20)	68.3 (60–81)	28.5 (13.5–40)
8	Lt MT (LA1-3, LH1-3, LBP1)	6	LH2, LBP1	200–250	17.3 (13.1–21.0)	56 (19–101)	1.47 (0.74–2.14)	65.7 (19–139)	21.0 (8–40)
9	Rt MT (RA1-2, RH2-3, RBA1, RBP1-2), Rt TP	5	RA1-2	200–333	35.8 (30.9–39.7)	31 (20–47)	0.8 (0.56–1.42)	55 (29–82)	11 (6–16)
10	Rt MT (RA1-2, RH1-3, RBP1-2)	3	RA1	200–250	26.1 (16.5–35)	32 (19–64)	0.84 (0.42–1.92)	48.7 (28–80)	13.3 (12–14)
11	Rt MT (RH1-2)	2	RH1	200–250	49.3 (11.8–89.7)	28 (25–38)	1.01 (0.4–2.18)	40.5 (38–43)	5 (0–10)
12	Lt MT (LA1-2, LH1-2)	2	-	-	-	-	-	-	-
13	Rt MT (RA1-2, RBP1-2)	1	-	-	-	-	-	-	-
14	Lt basal T (LH6, LBP5-6)	2	-	-	-	-	-	-	-
15	Rt MT (RH1, RBA1, RBP1)	1	-	-	-	-	-	-	-
16	Non-localizing	3	-	-	-	-	-	-	-
17	Lt T	2	-	-	-	-	-	-	-
18	Lt hemisphere	1	-	-	-	-	-	-	-
19	Lt basal T	2	-	-	-	-	-	-	-

Lt: left; Rt: right; Bil: bilateral; MT: medial temporal; TP: temporo-parietal; T: temporal.

3. Results

3.1. Characteristics of ictal HFO

A total of 58 seizures were recorded at 1 kHz sampling rate. The seizure onset zone identified on the conventional EEG recording; number of seizures recorded at 1 kHz sampling rate; electrodes detecting HFO; frequency, amplitude and duration of HFO; inter-HFO interval; total duration; and time lag from HFO onset to EEG seizure onset are shown in Table 2. Ictal HFO were detected in 11 patients. In nine of 11 patients with HFO, all seizures recorded at 1 kHz sampling originated from the medial temporal regions ipsilateral to the side of surgical resection. In Patient 2, independent seizure onset from the left and right medial temporal regions was recorded. In Patient 9, five seizures were recorded. Three seizures originated from the right medial temporal area, while the remaining two seizures arose from the right temporo-parietal area preceding the discharges in the right medial temporal area two to 3 days after withdrawal of carbamazepine. Medial temporal onset seizures and temporo-parietal onset seizures occurred on the same day. Finally, based on all the information, including intracranial EEG findings, all 11 patients with ictal HFO in the medial temporal area were diagnosed with MTLE and underwent resection surgery. Among the remaining eight patients in whom no HFO were detected in the medial temporal structures, only three were diagnosed with MTLE (patients 12, 13, and 15), while the seizure onset zones were heterogeneous or poorly localized in the others. In one patient with no ictal HFO recorded in the medial temporal lobe (Patient 19), ictal HFO were detected in the basal temporal area (electrodes LBA5 and LBP5). Conventional ictal EEG also revealed seizure onset in the left basal temporal region (LBA3-6, LBP3-6). Basal temporal language area was also identified in the same region (LBA2-4, LBP3). This patient did not undergo resection surgery, considering the risk of language deficit.

The HFO in all 11 patients were segmental, lasted 19–75 ms (mean value), were detected in 1–4 channels, and had frequencies of 200–333 Hz. HFO could not be detected outside this frequency range. In eight of 11 patients, HFO were detected at more than one electrode. The mean amplitudes of HFO ranged from 17.3 to 49.3 μV. They were localized in unilateral medial temporal structures, mainly in the hippocampus (Fig. 2), and/or the amygdala. In three patients (patients 4, 9, and 10), ictal HFO were exclusively detected in the amygdala. HFO were also detected by subdural electrodes placed over the mediobasal temporal region (parahippocampal gyrus, TB) in five patients. HFO detected by subdural electrodes always appeared simultaneously with the HFO detected by depth electrodes. The electrodes with ipsilateral HFO were included in the seizure onset zone defined by conventional EEG in 10 patients. In the remaining patient (Patient 3), the electrodes with HFO were outside the seizure onset zone. However, both the electrodes with HFO and seizure onset zone of the patient were included in the left medial temporal structures and resected together by amygdalohippocampectomy.

HFO (ipsilateral to the side of surgical resection) onset preceded conventional EEG ictal onset by 5.0–74.5 s (mean values). The characteristics of HFO were consistent among seizures in each patient.

Ictal HFO were usually associated with spikes. When HFO were associated with spikes, they followed the peaks of the spikes. The

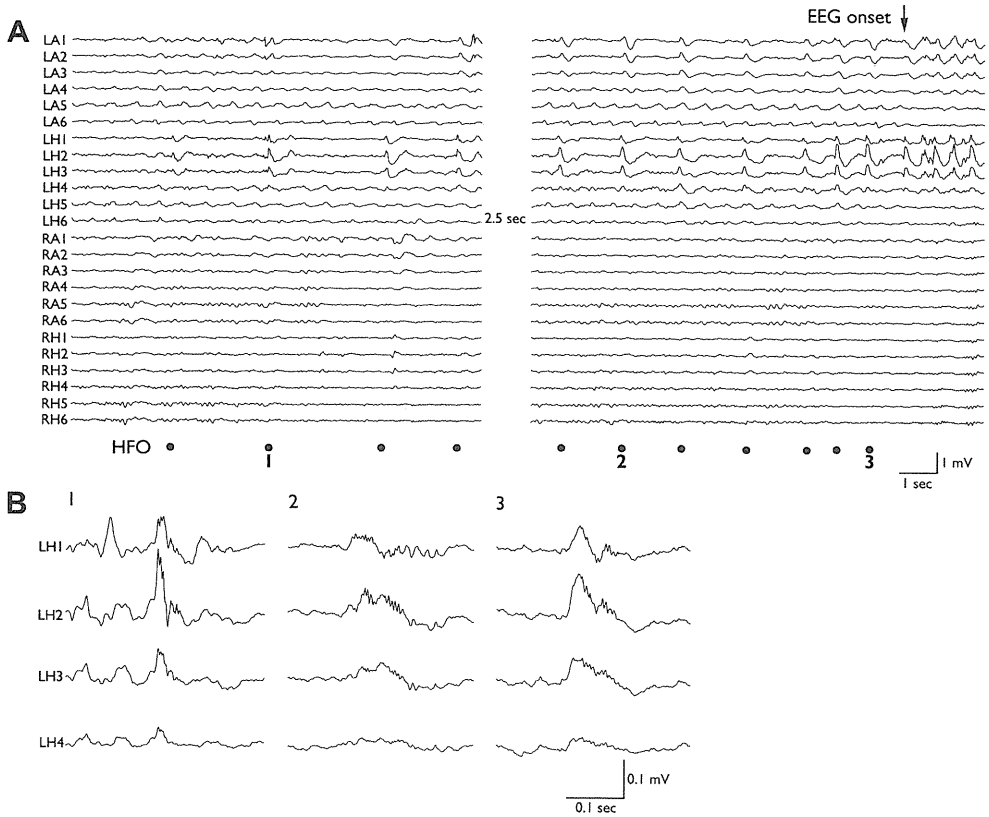

Fig. 2. Ictal EEG and HFO in Patient 1. (A) Conventional EEG (low-pass filter 120 Hz, time constant 0.1 s) reveals periodic sharp waves at LH1-3. The periodic sharp waves are followed by more repetitive sharp waves in the left hippocampus and amygdala. Filled circles indicate the presence of HFO. (B) HFO waveforms (low-pass filter 300 Hz, time constant 0.003 s). 200–250 Hz high frequency activities are detected at LH1-3. Note the calibration, which shows that HFO waves have very small amplitude and short duration.

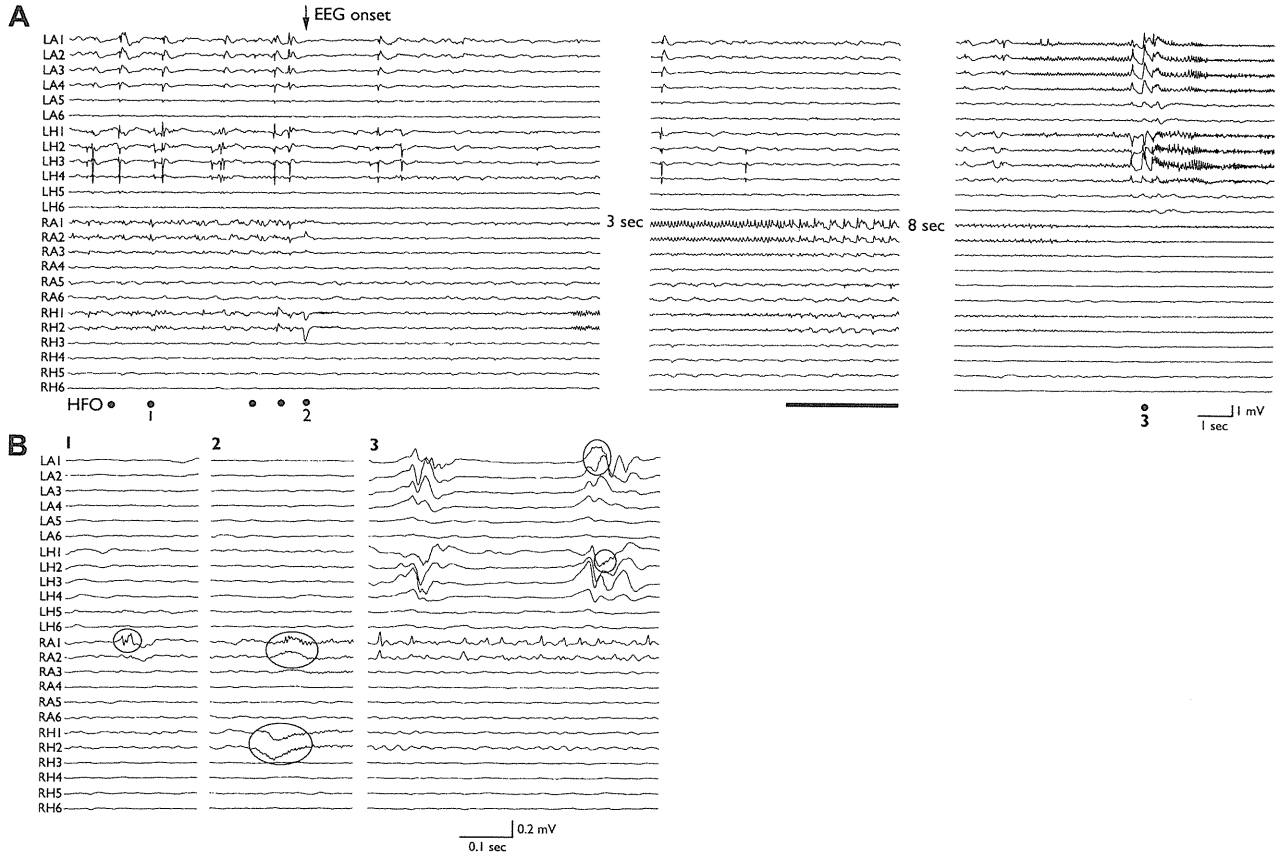

Fig. 3. Ictal EEG and HFO in Patient 7. (A) On conventional EEG (low-pass filter 120 Hz, time constant 0.1 s), ictal EEG starts with a large positive sharp wave at RH1 and RH2, followed by beta activities at the same electrodes. Seven seconds later, rhythmic beta waves start at RA1 and RA2 with gradual evolution. Approximately 45 s later, left-sided electrodes (LH1-4 and LA1-4) start showing small spikes, followed by beta activities in the same electrodes Filled circles and the bold line indicate the presence of HFO. (B) HFO waveforms before conventional EEG onset, around onset, and around conventional EEG onset at the left hemisphere (low-pass filter 300 Hz, time constant 0.003 s). These demonstrate 200–333 Hz high-frequency activities at 1–4 electrodes in the right side (RA1, RA2, RH1 and RH2). These also demonstrate high-frequency activities at LA1-2 and LH1 around the conventional EEG onset on the left side. Circles indicate the locations of HFO.

mean total duration of ictal HFO ranged from 28.8 to 79.5 s. Contralateral seizure propagation was seen in 10 of 11 patients with ictal HFO. Except for one patient (Patient 7), HFO were not detected in the areas of contralateral seizure propagation. In Patient 7, three seizures were recorded at 1 kHz sampling rate. All seizures originated from the right medial temporal region, and propagated to the left side. Ictal HFO were detected by the right medial temporal electrodes (RA1-2, RH1-2). In this exceptional case, ictal HFO were also detected in the left medial temporal electrodes (LA1-2, LH1) in two of three seizures. HFO on the left side were observed only two or three times, and the total durations of these contralateral HFO were 0.36–0.64 s, much shorter than those of HFO recorded on the resection side (Fig. 3).

In another patient (Patient 2), five seizures were recorded at 1 kHz sampling rate. On conventional EEG, three of five seizures originated from the right medial temporal region, and the remaining two from the left medial temporal region. Ictal HFO in the right medial temporal structures were observed in the three seizures originating on the right. Even in the two seizures originating from the left side, ictal HFO were detected only in the right medial temporal structures and preceded the left temporal EEG onset by 74.5 s (Fig. 4).

Interictal HFO were also detected in 10 patients (Patients 2–5, 7–11, and 18) (Table 3). These interictal HFO appeared more irregularly, and the inter-burst intervals of HFO lasted longer than those of ictal HFO. In eight patients, interictal HFO were detected only on the side of resection. In one patient (Patient 11), interictal HFO were detected in bilateral hippocampi, although the frequency of appearance was much higher on the ipsilateral side. In the remaining patient who did not proceed to surgery (Patient 18), interictal HFO were detected in the unilateral medial temporal structure.

3.2. Ictal HFO and hippocampal pathology

Surgical procedures and hippocampal pathology are shown in Table 4. In 11 patients who had ictal HFO, histological examination revealed HS in all the patients (type 1a in nine, and type 2 in two). In three patients (Patients 4, 9, and 10) showing ictal HFO exclusively in the amygdala, HS (type 1a) was also identified histologically. In eight patients who showed no ictal HFO, five underwent medial temporal resection (amygdalohippocampectomy in three, anterior temporal lobectomy including medial temporal structures in two), and pathological results were available in four of five patients. Classic sclerosis (type 1a) was observed in one patient, while no HS was found in the remaining three patients. The association between the presence of ictal HFO and HS was statistically significant ($p = 0.008791$).

3.3. Ictal HFO and postoperative seizure outcome

Favorable seizure outcome (Engel's class I) was obtained in eight of 11 patients with ictal HFO (Table 4). In one patient with class II outcome (Patient 11), a few seizures were observed soon

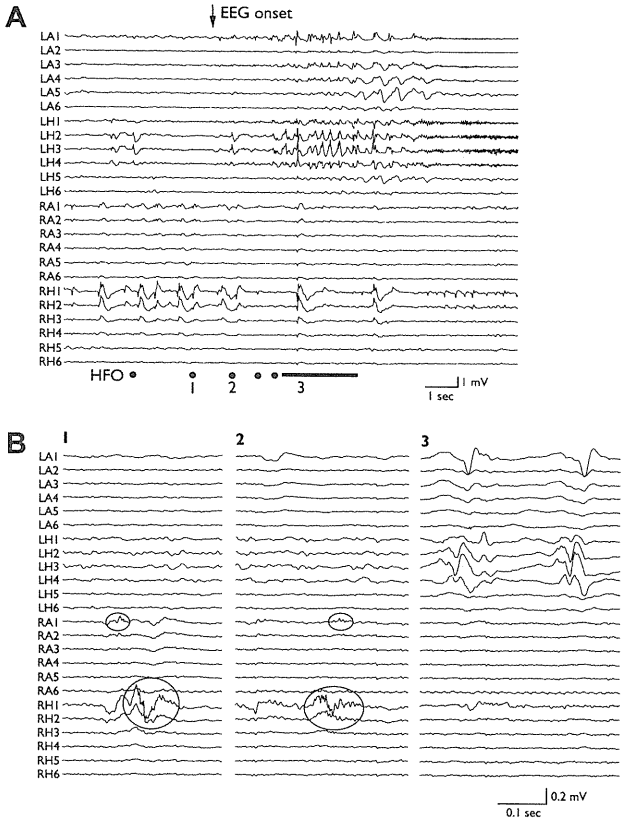

Fig. 4. Ictal EEG and HFO in Patient 2. (A) On conventional EEG (low-pass filter 120 Hz, time constant 0.1 s), ictal EEG starts with repetitive spikes at LA1, LH2, LH3, and LH4, as well as rhythmic alpha activity at LH1 at the same time. The spikes spread widely in the left temporal area, and are replaced by rhythmic beta waves at LH1, LH2, LH3, and LH4. The right hemispheric electrodes do not show clear ictal activities throughout. Filled circles and bold line indicate the presence of HFO. (B) HFO waveforms before conventional EEG onset, and around onset (low-pass filter 300 Hz, time constant 0.003 s). 200–333 Hz high frequency activities are recorded at 1 to 3 electrodes on the right side (RA1, RH1, and RH2). Circles indicate the locations of HFO. Although spikes are seen on the left side, HFO is not recorded at the left-sided electrodes.

after surgery, and the seizures were controlled by increasing antiepileptic medications. In one patient (Patient 9) with poor outcome (class III), seizures arising from contralateral temporal region were documented postoperatively. The reason for unfavorable outcome in the remaining patient (Patient 3) was unclear. Among the three cases with ictal HFO restricted to amygdala (Patients 4, 9, and 10), favorable outcome was obtained in two, and unfavorable outcome in one. Favorable seizure outcome (Engel's class I) was obtained in three of five patients without HFO who underwent resective surgery including medial temporal structures. Comparing the patients who underwent amygdalohippocampectomy in the two groups, favorable seizure outcome was obtained in seven of 10 patients with ictal HFO, and in two of three patients without HFO. Seizure outcome was not statistically different between the patients with and without ictal HFO.

4. Discussion

4.1. Characteristics of ictal HFO in medial temporal lobe

HFO in medial temporal structures have been reported in recent years. Most reports of HFO in patients with MTLE analyzed the interictal state with microelectrodes, usually during non-REM sleep (Staba et al., 2004). Fast ripples are considered to represent hypersynchronous discharges of locally interconnected principle neurons capable of generating spontaneous seizures (Staba et al., 2002). Fast ripples are most often recorded on a single microwire, supporting the hypothesis that fast ripple HFO are primarily generated by highly localized, sub-millimeter scale neuronal assembles that are most effectively sampled by microwire electrodes (Worrell et al., 2008). However, other reports have demonstrated that macroelectrodes also detect HFO in medial temporal structures (Jirsch et al., 2006; Khosravani et al., 2009; Yamaguchi et al., 2008). Although interictal HFO in the medial temporal lobe have been widely studied, the clinical significance of 'ictal' HFO in the medial temporal lobe has not been specifically studied.

In this study, multiple sites of the medial temporal regions were investigated with both depth and subdural electrodes. Ictal HFO appeared in a relatively stereotyped segmental fashion, and were detected mainly in the hippocampus and/or the amygdala. They were mostly located unilaterally ipsilateral to the side of HS, in contrast to interictal HFO in medial temporal lobe, which can be detected bilaterally (Staba et al., 2002). In eight patients, ictal HFO were detected at multiple electrode contacts, suggesting that HFO may reflect synchronous discharges widely located within unilateral medial temporal region. The sensitivity of subdural electrodes in detecting HFO was lower than that of depth electrodes.

Table 3
Detection and parameters of interictal high frequency oscillations.

Patient	Electrodes detecting HFO	Frequency (Hz)	Amplitude (μV)	Duration (ms)	Inter-HFO Interval (s)
1	None	–	–	–	–
2	RH1-2	200–333	48.5 (30.9–70.6)	31 (33–71)	24.4 (6.4–42.9)
3	LH2-3	200–333	42.7 (17.6–61.8)	25 (19–28)	1.5 (0.3–3.3)
4	RA1	200–333	25.0 (10.3–88.2)	30 (18–43)	12.1 (1.4–73)
5	LA1-2, LBP1-2	200–333	39.5 (22.6–55.8)	23 (16–32)	2.5 (0.4–17.9)
6	None	–	–	–	–
7	RA1	200–333	42.7 (20.6–85.3)	22 (13–34)	18.3 (10.6–23.7)
8	LH2, LBP1	200–250	29.4 (26.5–35.3)	50 (29–67)	4.3 (1.6–18.7)
9	RA1-2	200–333	32.0 (12.0–39.7)	25 (19–34)	2.41 (0.4–6.8)
10	RA1	200–250	29.4 (20.6–38.2)	19 (15–25)	27.8 (3.6–121)
11	RH1	200–250	57.8 (44.1–76.5)	26 (10–46)	4.3 (0.8–16.3)
	LH2	200–250	35.3 (26.5–44.1)	20 (17–23)	90 (40–199)
12	None	–	–	–	–
13	None	–	–	–	–
14	None	–	–	–	–
15	None	–	–	–	–
16	None	–	–	–	–
17	None	–	–	–	–
18	LH1–2, LBP1–2	200–333	26.8 (13.2–41.2)	27 (22–32)	31 (1–131)
19	None	–	–	–	–

Table 4
Surgery, hippocampal pathology, and seizure outcome in 19 patients.

Patient	Surgery	Follow-up (months)	MRI	Pathology (Blűmcke)	Outcome (Engel)
1	Lt AHE	49	Lt HS	HS (Type 1a)	Ia
2	Rt AHE	51	Rt HS	HS (Type 1a)	Id
3	Lt AHE	13	Lt HS	HS (Type 1a)	IIIa
4	Rt AHE	43	Rt HS	HS (Type 1a)	Ic
5	Lt ATL	33	Lt HS	HS (Type 1a)	Id
6	Lt AHE	12	Lt HS	HS (Type 2)	Ia
7	Rt AHE	22	Rt HS	HS (Type 2)	Ia
8	Lt AHE	26	Lt HS	HS (Type 1a)	Ib
9	Rt AHE	24	Rt HS	HS (Type 1a)	IIIa
10	Rt AHE	12	Rt HS	HS (Type 1a)	Ia
11	Rt AHE	17	Normal	HS (Type 1a)	IIb
12	Lt AHE	54	Normal	No HS	IIb
13	Rt AHE	35	Rt AH	No HS	Ia
14	Lt LTR	37	Normal	NA	IIIa
15	Rt AHE	48	Rt HS	HS (Type 1a)	Ic
16	Lt ATL	40	Normal	No HS	Ia
17	Lt ATL	24	Normal	NA	IIIa
18	No	–	Lt HS	–	–
19	No	–	Normal	–	–

Rt: right; Lt: left; AHE: amygdalohippocampectomy; ATL: anterior temporal lobectomy; LTR: lateral temporal resection; HS: hippocampal sclerosis; AH: amygdalar hypertrophy; NA: data not available.

Depth electrodes were inserted into subiculum, Ammon's horn, and amygdala, whereas subdural electrodes were implanted over the parahippocampal gyrus. One reason for the different sensitivity may be the different locations of the electrodes. Subiculum, Ammon's horn, and amygdala may generate ictal HFO more frequently than parahippocampal areas. Another reason may be the wider contact surface of subdural electrode (4.15 mm^2) than that of depth electrode (2.6 mm^2, calculated from the diameter and the length). In addition to the location of electrodes, the difference in contact surface of the electrodes may affect the sensitivity.

In 10 of 11 patients with ictal HFO, the electrodes with ipsilateral ictal HFO were included in the seizure onset zone, whereas in the remaining patient, they were outside the seizure onset zone. Since both the areas with HFO and seizure onset zone were resected, whether HFO or seizure onset zone is superior for deciding the area of resection cannot be determined.

Usually, HFO followed the peaks of the spikes. In a separate study of neocortical epilepsy, we found that very high frequency activities faster than 1000 Hz usually preceded the spikes. In other words, spikes seem to interrupt very high frequency activities in neocortical epilepsy. Therefore, we speculate that spikes may be an inhibitory phenomenon in neocortical epilepsy (Usui et al., 2010). On the contrary, the temporal relation between spikes and HFO in the medial temporal lobe suggests that the spikes may trigger HFO. Therefore, spikes may be an excitatory phenomenon in MTLE.

In a conventional EEG setting, inter-observer differences are common even for the interpretation of ictal onset, since conventional EEG waveforms can be very variable. On the contrary, the characteristics of medial temporal ictal HFO were very consistent among patients. Therefore, the identification of ictal HFO may support interpretation of ictal EEG.

Ictal HFO (ipsilateral to the side of surgical resection) always appeared before conventional EEG seizure onset. Except in one patient, ictal HFO did not appear in the region of contralateral spread. Moreover, they did not spread outside the medial temporal regions. These findings suggest that HFO are strongly related to epileptogenicity. Jirsch et al. (2006) also reported concordant results. In one exceptional case, HFO appeared in the area of contralateral seizure spread, but the total duration of contralateral HFO was much shorter. In this case, amygdalohippocampectomy on the side of seizure origin was performed, and the patient has been seizure free for approximately 2 years. Careful follow-up of this patient is necessary to evaluate epileptogenicity in the contralateral medial temporal lobe.

Temporal lobe epilepsy has been considered as a bilateral disease (Margerison and Corsellis, 1966). It is often difficult to decide the surgical indication and the side of resection in patients with bitemporal epilepsy, even with intracranial EEG. In one patient, clinical seizures originated independently from bilateral medial temporal lobes when assessed on conventional EEG. However, ictal HFO were detected unilaterally. The findings in this patient strongly suggest that ictal HFO may not be just a part of ictal EEG changes, but probably represent electrophysiological phenomena independent of the activity usually detected by conventional EEG, and that epileptogenicity and ictogenicity could be differentiated by ictal HFO. Crépon et al. (2010) recently studied interictal HFO with macroelectrodes, and reported detection of interictal HFO unilaterally in a case of bitemporal seizure onset. They suggested the usefulness of interictal HFO for defining the seizure onset zone. In our patients, interictal HFO were detected in 10 patients, and they were unilateral and ipsilateral to the side of resection in eight patients. Therefore, interictal HFO may be also useful for deciding the side of resection. However, interictal HFO in medial temporal lobe has also been detected bilaterally (Staba et al., 2002). The one reason for disagreement may be the extended periods of recording in the study by Staba et al. (2002) (the mean length of time analyzed was 177 ± 7 min of non-REM sleep) compared with our study (5 min). Further studies are necessary for clarifying the usefulness of ictal and interictal HFO for deciding the side of resection in bitemporal epilepsy.

4.2. Correlation with hippocampal pathology

Using microelectrodes, Staba et al. (2007) reported that higher fast ripples to ripple ratios are associated with histopathologic changes found in HS in TLE patients. Recently, Ogren et al. (2009) studied interictal HFO recorded by hippocampal microelectrodes in 10 patients with MTLE, and demonstrated the proximity between fast ripples and local hippocampal atrophy. Our study demonstrated a strong association between ictal HFO (fast ripple range) in medial temporal lobe detected by macroelectrodes and HS. In Patient 11, preoperative MRI did not reveal clear HS. However, ictal HFO were detected in the right hippocampal electrode and HS was detected pathologically. Ictal HFO in the medial temporal lobe may be the electrophysiological signature of HS. Neuron loss and synaptic reorganization may contribute to the generation of HFO (Ogren et al., 2009).

Among the four patients without ictal HFO who underwent resection of the medial temporal lobe, histopathology revealed no HS in three of four patients. In Patient 13 with no HS, amygdalohippocampectomy was performed and the patient became seizure free. Ictal HFO may be absent in patients with MTLE without HS. In one patient who had HS (classic sclerosis) but no HFO (Patient 15), seizures continued with somatomotor signs for 2 years after amygdalohippocampectomy, and then became controlled without medication adjustment, and she has been seizure-free for more than 2 years (Engel's class Ic). Although the reason for late seizure remission in this patient is not clear, the epileptogenic zone might not be restricted to medial temporal structures. In addition to HS, primary epileptogenicity in the medial temporal lobe may be a requisite for generating ictal HFO.

4.3. Correlation with postoperative seizure outcome

Eight of 11 patients with HFO achieved Engel's class I outcome, and one patient had class II outcome. In one case (Patient 9), contralateral temporal onset seizures were recorded after surgery, although contralateral HFO was never recorded during invasive monitoring. Although an association between resection of ictal HFO generating zone and favorable seizure outcome in neocortical epilepsy has been suggested (Ochi et al., 2007), such a relationship could not be proven in this study. However, this result should be interpreted with caution. A strong association with ictal HFO and HS was established in this study. All patients with ictal HFO were diagnosed with MTLE. Subsequently, seven of 10 patients with HFO who underwent amygdalohippocampectomy obtained good seizure outcome. On the contrary, only three of eight patients without HFO were diagnosed with MTLE. In other patients, the epileptogenic zone was heterogeneous or poorly localized. The presence of ictal HFO in the medial temporal lobe strongly favors a diagnosis of MTLE with HS and subsequent resective surgery. The small number of patients without HFO may lead to the negative result for seizure outcome. Further study including more patients without HFO may clarify the relationship between the presence of ictal HFO and postoperative seizure outcome.

Jacobs et al. (2010) analyzed interictal HFO in 20 patients, and compared rates and extents of HFO in resected and non-resected areas with surgical outcome. Patients with a good outcome (Class I or II) had a significantly larger proportion of HFO-generating areas removed than patients with a poor outcome (Class III or IV). In our 11 patients with ictal HFO, HFO-generating areas were completely resected in all 11 patients. However, there were two patients with a poor outcome (Class III). The discordance may be due to the fact that Jacobs et al. included both fast ripples and ripples as HFO, whereas we did not include ripples as HFO. Ripples can be either pathologic or memory-related. Further studies for differentiating pathological ripples from healthy, memory-related ones are necessary.

4.4. Clinical significance of absence of HFO in the medial temporal lobe

In eight patients, no ictal HFO was detected in the medial temporal lobe. Compared to patients with HFO, the epileptogenic zones of patients without HFO were more heterogeneous or poorly localized.

When no ictal HFO is detected in the medial temporal area, two possibilities should be considered. One is that the diagnosis is not MTLE. In Patient 16, lateral temporal lobe epilepsy was diagnosed and left anterior temporal lobectomy, including medial temporal lobe, was performed with complete seizure control, and histopathology revealed no HS. In this case, absence of ictal HFO in the medial temporal lobe may simply reflect that the medial temporal lobe might not be included in the epileptogenic zone. In Patient 19 with no HFO in the medial temporal lobe, ictal HFO were detected in the basal temporal lobe. Ictal high frequency activities recorded from neocortex have been reported (Jirsch et al., 2006; Ochi et al., 2007; Usui et al., 2010). However, most of the patients in this study were diagnosed with possible temporal lobe epilepsy. Therefore neocortical HFO was not common. Another possibility is that the diagnosis is MTLE without HS. In Patient 13, amygdalohippocampectomy resulted in seizure control, and histopathology revealed no HS. Therefore, in some patients with MTLE without HS, ictal HFO may not be detected. Although further research is needed, ictal HFO in the medial temporal lobe may be a specific marker for MTLE with HS.

References

Blümcke I, Pauli E, Clusmann H, Schramm J, Becker A, Elger C, Merschhemke M, Meencke H, Lehmann T, Von Deimling A, Scheiwe C, Zentner J, Volk B, Romstöck J, Stefan H, Hildebrandt M. A new clinico-pathological classification system for mesial temporal sclerosis. Acta Neuropathol. 2007;113:235–44.

Bragin A, Engel J, Wilson CL, Fried I, Buzsáki G. High-frequency oscillations in human brain. Hippocampus 1999;9:137–42.

Bragin A, Wilson CL, Staba RJ, Reddick M, Fried I, Engel Jr J. Interictal high-frequency oscillations (80–500 Hz) in the human epileptic brain: entorhinal cortex. Ann. Neurol. 2002;52:407–15.

Crépon B, Navarro V, Hasboun D, Clemenceau S, Martinerie J, Baulac M, Adam C, Le Van Quyen M. Mapping interictal oscillations greater than 200 Hz recorded with intracranial macroelectrodes in human epilepsy. Brain 2010;133:33–45.

Gastaut H., Fischer-Williams, M. The physiopathology of epileptic seizures. American Physiological Society, Handbook of Physiology: A critical, comprehensive presentation of physiological knowledge and concepts. American Physiological Society, Washington DC, 1959, pp. 329–363.

Jacobs J, Zijlmans M, Zelmann R, Chatillon C-E, Hall J, Olivier A, Dubeau F, Gotman J. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann. Neurol. 2010;67:209–20.

Jirsch JD, Urrestarazu E, Levan P, Olivier A, Dubeau F, Gotman J. High-frequency oscillations during human focal seizures. Brain 2006;129:1593–608.

Khosravani H, Mehrotra N, Rigby M, Hader W, Pinnegar CR, Pillay N, Wiebe S, Federico P. Spatial localization and time-dependent changes of electrographic high frequency oscillations in human temporal lobe epilepsy. Epilepsia 2009;50:605–16.

Lüders H, Acharya J, Baumgartner C, Benbadis S, Bleasel A, Burgess R, Dinner DS, Ebner A, Foldvary N, Geller E, Hamer H, Holthausen H, Kotagal P, Morris H, Meencke HJ, Noachtar S, Rosenow F, Sakamoto A, Steinhoff BJ, Tuxhorn I, Wyllie E. Semiological seizure classification. Epilepsia 1998;39:1006–13.

Margerison JH, Corsellis JAN. Epilepsy in the temporal lobes. Brain 1966;89:499–530.

Mihara T, Baba K. Combined use of subdural and depth electrodes. In: Lüders HO, Comair YG, editors. Epilepsy surgery. second ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 613–21.

Mihara T, Matsuda K, Tottori T, Baba K, Inoue Y, Hiyoshi T, Watanabe Y, Yagi K, Seino M. Conditions for omitting intracranial long-term monitoring before surgical resection in patients with temporal lobe epilepsy. Jpn. J. Psychiatry Neurol. 1992;46:323–9.

Ochi A, Otsubo H, Donner EJ, Elliott I, Iwata R, Funaki T, Akizuki Y, Akiyama T, Imai K, Rutka JT, Snead III OC. Dynamic changes of ictal high-frequency oscillations in neocortical epilepsy: using multiple band frequency analysis. Epilepsia 2007;48:286–96.

Ogren JA, Wilson CL, Bragin A, Lin JJ, Salamon N, Dutton RA, Luders E, Fields TA, Fried I, Toga AW, Thompson PM, Engel Jr J, Staba RJ. Three-dimensional surface maps link local atrophy and fast ripples in human epileptic hippocampus. Ann. Neurol. 2009;66:783–91.

Spencer SS, Guimaraes P, Katz A, Kim J, Spencer D. Morphological patterns of seizures recorded intracranially. Epilepsia 1992;33:537–45.

Staba RJ, Wilson CL, Bragin A, Fried I, Engel Jr J. Quantitative analysis of high-frequency oscillations (80–250 Hz) recorded in human epileptic hippocampus and entorhinal cortex. J. Neurophysiol. 2002;88:1743–52.

Staba RJ, Wilson CL, Bragin A, Jhung D, Fried I, Engel Jr J. High-frequency oscillations recorded in human medial temporal lobe during sleep. Ann. Neurol. 2004;56:108–15.

Staba RJ, Frighetto L, Behnke E, Mathern GW, Fields T, Bragin A, Ogren J, Fried I, Wilson CL, Engel Jr J. Increased fast ripple to ripple ratios correlate with reduced hippocampal volumes and neuron loss in temporal lobe epilepsy patients. Epilepsia 2007;48:2130–8.

Usui N, Terada K, Baba K, Matsuda K, Nakamura F, Usui K, Tottori T, Umeoka S, Fujitani S, Mihara T, Inoue Y. Very high frequency oscillations (over 1000 Hz) in human epilepsy. Clin. Neurophysiol. 2010;121:1825–31.

Worrell GA, Gardner AB, Stead SM, Hu S, Goerss S, Cascino GJ, Meyer FB, Marsh R, Litt B. High-frequency oscillations in human temporal lobe: simultaneous microwire and clinical macroelectrode recordings. Brain 2008;131:928–37.

Yamaguchi M, Terada K, Baba K, Nakamura F, Inoue Y. Ictal high frequency oscillations in patients with mesial temporal lobe epilepsy. Jpn. J. Clin. Neurophysiol. 2008;36:615–23.