Chapter 2
Examinations for Clinical Practice of Epilepsy

CQ 2-1

How useful is EEG for the diagnosis of epilepsy?

Summary

Electroencephalography (EEG) is the most useful clinical examination for the diagnosis of epilepsy. In a considerable number of patients, however, epileptic discharges cannot be detected by only a single routine EEG examination, and multiple EEG recordings including sleep or sleep-deprived EEG are required.

Comment

Diagnosis of epilepsy is conducted in accordance with the International League Against Epilepsy (ILAE) classification of epileptic seizure types (1981) as well as classification of epilepsies, epileptic syndromes and related seizure disorders (1989). Thus, EEG findings are essential in addition to clinical seizure types and neurological symptoms. Regarding the EEG recording methods, it is desirable to follow the guidelines of the Japanese Society of Clinical Neurophysiology [1].

However, in a considerable number of patients, seizure discharges cannot be detected by a single routine EEG examination. In a systematic review of 12 articles with evidence levels of classes I and II [as defined by the American Academy of Neurology (AAN)] comprising 1,766 adult patients, approximately 50% of the patients with epilepsy had normal EEG [2]. Regarding the question of how many EEG examinations are needed to exclude a diagnosis of epilepsy, there is no solid evidence-based answer. However, some reports indicate that the more EEG examinations are repeated, the higher is the epileptic discharges detection rate on EEG [3].

In addition, the diagnostic value of sleep EEG is high. In patients in whom no epileptic discharges are detected in awake recordings, epileptic discharges are often detected by sleep EEG [3]. Especially, it has been reported that during sleep, the epileptic discharges detection rate is higher in children than in adults, and higher for partial epilepsy than for generalized epilepsy.

However, even if epileptic discharges are recorded in EEG, unless the discharges can explain the seizure symptom, this finding alone does not necessarily lead to a diagnosis of epilepsy. Abnormal EEG activity is also seen in some normal persons, and one paper reported that epileptiform discharges were recorded in 0.5% (69/13,658) of normal persons [3].

A recent systematic review of 15 articles with a total of 1,799 patients presenting with a first unprovoked seizure analyzed the (1) sensitivity (percentage of patients with epileptiform discharges on routine EEG among those who had repeated seizures during one-year follow-up and hence were diagnosed with epilepsy) and (2) specificity (percentage of patients finally diagnosed with epilepsy among those who were found to have epileptiform discharges on routine EEG) separately in children and adults [4]. In adults, (1) sensitivity was 17.3% and (2) specificity was 94.7%. In children, (1) sensitivity was 58.7% and (2) specificity was 69.6%.

■ References

1) Japanese Society of Clinical Neurophysiology, Clinical Electroencephalography Examination Standards Revision Committee. Revised clinical electroencephalography examination standards, 2002. Japanese Journal of Clinical Neurophysiology. 2003; 31(2): 221-242 (in Japanese). http://jscn.umin.ac.jp/files/guideline/ClinicalEEGtest.pdf (in Japanese).
2) Krumholz A, Wiebe S, Gronseth G, et al. Practice Parameter: Evaluating an apparent unprovoked first seizure in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2007; 69(21): 1996-2007.
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■ Search formula and secondary reference sources

PubMed search: November 8, 2008

epilepsy [majr] AND (electroencephalography [majr] OR "brain wave" OR "brain waves") AND classification AND ("sensitivity and specificity" [mh] OR diagnostic errors [mh] OR sensitivity [tiab] OR specificity [tiab] OR predictive value* OR likelihood ratio* OR false negative* OR false positive* OR controlled clinical trial [pt] OR randomized controlled trial [pt] OR double blind method [mh] OR single blind method [mh] OR practice guideline [pt] OR diagnosis, differential [mh] OR consensus development conference [pt] OR random* [tiab] OR random allocation [mh] OR single blind* [tiab] OR double blind* [tiab] OR triple blind* [tiab] OR likelihood functions [mh] OR area under curve [mh] OR reproducibility of results [mh] OR meta-analysis [mh] OR meta-analysis [pt] OR metaanaly* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review* OR systematic [sb]) = 150

No references that could serve as evidence were found in Ichushi Web.

Additional PubMed search: July 1, 2015

(epilepsy/diagnosis [MeSH Major Topic]) AND Electroencephalography [MeSH] Filters: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 85

No references that could serve as evidence were found in Ichushi Web.

CQ 2-2

What is the significance of EEG examination in the treatment of epilepsy?

Summary

Generally, EEG examination is useful for the evaluation of therapeutic effect and prognosis of epilepsy.

Comment

Many reports have shown that EEG examination is generally useful for the evaluation of the therapeutic effect and the prognosis of epilepsy. In the treatment of epilepsy patients, it is important to follow the pattern of appearance of epileptic discharges and their frequency over time [1, 2]. In particular, in patients with absence seizure, since the occurrence rate of 3-Hz spike-and-wave complex on EEG reflects the disease severity, it is useful to do follow-up EEG in order to monitor the therapeutic effect [3]. Also, the type of epilepsy may change, and EEG examination is useful to capture this change [3]. However, there is a lack of clear evidence on these issues, and epilepsy patients do not always show abnormal findings in EEG examinations. On the other hand, even if epileptiform discharges are detected, if they are interictal abnormalities and the patient is clinically seizure-free, we do not always need to increase the drug dose or add a new antiepileptic drug. Hence, we should interpret EEG findings during the treatment process taking into account the clinical course and other findings. Furthermore, regarding the question of how often EEG examination should be done during epilepsy treatment, there is no solid evidence.

■ References

1) Fowle AJ, Binnie CD. Uses and abuses of the EEG in epilepsy. Epilepsia. 2000; 41(Suppl 3): S10-18.
2) Krumholz A, Wiebe S, Gronseth G, et al. Practice parameter: evaluating an apparent unprovoked first seizure in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2007; 69(21): 1996-2007.
3) Binnie CD, Stefan H. Modern electroencephalography: its role in epilepsy management. Clin Neurophysiol. 1999; 110(10): 1671-1697.

■ Search formula and secondary reference sources

PubMed search: October 30, 2008
(epileptic seizures OR epilepsy) AND diagnosis AND "electroencephalography" [MeSH Terms] AND ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio* OR practice guideline [pt] OR likelihood functions [mh]) AND (meta-analysis [mh] OR meta-analysis [pt] OR metaanaly* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review* OR systematic [sb]) = 125

No references that could serve as evidence were found in Ichushi Web.

Additional PubMed search: July 2, 2015
((epilepsy [MeSH Major Topic]) AND Electroencephalography [MeSH Major Topic] AND (Monitoring, Physiologic [Mesh] OR monitor*)) Filters: Guideline; Meta-Analysis; Randomized Controlled Trial; Clinical Trial; Publication date from 2008/01/01 to 2015/12/31; Humans; Japanese; English = 27

No references that could serve as evidence were found in Ichushi Web.

CQ 2-3

What is the significance of long-term video-EEG monitoring in clinical practice of epilepsy?

Summary

Long-term video-electroencephalography (VEEG) monitoring is a useful examination for making a definitive diagnosis of epilepsy, diagnosis of seizure type, and localization of epileptogenic zone.

Comment

Long-term video-electroencephalography (VEEG) monitoring examination simultaneously records video and EEG throughout 24 hours of a day, usually for several days [1]. The main purpose of this examination is to record "habitual seizures". While seizures are recorded at a rate of 2.5–7% in routine EEG examinations, reports have shown that seizures are recorded in 70–85% of the patients when VEEG is performed for 3.5–6 days [1, 2].

By analyzing the video (seizure symptoms) and EEG (ictal EEG findings), the following can be achieved: (1) differentiation of epileptic seizure from non-epileptic seizure; (2) in the case of epileptic seizure, differentiation of generalized seizure from partial seizure; (3) in the case of focal seizure, localization of epileptogenic zone [3]. Recordings for long duration sometimes reveal seizures not accompanied by clinical symptoms and interictal abnormalities not usually captured by routine EEG. The results of the VEEG study may greatly advance the diagnosis and treatment strategy or change them considerably. According to previous reports, the diagnosis and therapeutic strategy were altered in 55–60% of the patients who underwent VEEG [1-3]. Patients suspected of being refractory to drug therapy should undergo VEEG examination in a specialized facility [4]. VEEG is not only important in localization of the epileptogenic zone for epilepsy surgery, but is also useful for making a definitive diagnosis of epilepsy and defining the disease type.

■ References

1) Michel V, Mazzola L, Lemesle M, et al. Long-term EEG in adults: sleep-deprived EEG (SDE), ambulatory EEG (Amb-EEG) and long-term video-EEG recording (LTVER). Neurophysiol Clin. 2015; 45(1): 47-64.
2) Ghougassian DF, d'Souza W, Cook MJ, et al. Evaluating the utility of inpatient video-EEG monitoring. Epilepsia. 2004; 45(8): 928-932.
3) Yogarajah M, Powell HW, Heaney D, et al. Long term monitoring in refractory epilepsy: the Gowers Unit experience. J Neurol Neurosurg Psychiatry. 2009; 80(3): 305-310.
4) Labiner DM, Bagic AI, Herman ST, et al. Essential services, personnel, and facilities in specialized epilepsy centers—revised 2010 guidelines. Epilepsia. 2010; 51(11): 2322-2333.

■ Search formula and secondary reference sources

PubMed search: July 2, 2015
("epilepsy/diagnosis" [MeSH Major Topic]) AND (("video recording" [MeSH Terms]) OR ((Monitoring, Physiologic [Mesh] OR monitor*)))
Filters: Clinical Trial; Guideline; Randomized Controlled Trial; Meta-Analysis; Publication date from 2000/01/01 to 2015/12/31; Humans; English; Japanese = 77

No references that could serve as evidence were found in Ichushi Web.

CQ 2-4

What are the essential neuroimaging studies for clinical practice of epilepsy?

Summary

In the diagnosis of epilepsy, it is necessary to perform magnetic resonance imaging (MRI) or computed tomography (CT). MRI is especially useful in the diagnosis of partial epilepsy.

Comment

MRI or CT examination is essential for the diagnosis of epilepsy [1-3]. However, this does not apply to idiopathic generalized epilepsy or idiopathic partial epilepsy, because organic lesions are rarely found in these epilepsies. Although there is no class I and II evidence based on direct comparison between MRI and CT, MRI is considered to have higher diagnostic utility than CT, and is the first choice among several imaging studies [1]. Especially when making a diagnosis of partial epilepsy, MRI is a requisite. However, CT is preferable in the case of emergency, when the patient has a contraindication for MRI, or when a calcified lesion is suspected [4].

Specifically, the "practical clinical definition of epilepsy" reported by ILAE in 2014 recommends making a diagnosis of epilepsy in patients presenting with a first unprovoked seizure in whom MRI or CT examination shows organic lesions suggesting stroke, central nervous system infection, and traumatic brain injury, even though they have experienced only one seizure episode [2], because these patients have a high risk of seizure recurrence.

Regarding MRI imaging methods, fluid attenuated inversion recovery (FLAIR) images are useful in addition to the conventional T1-weighted and T2-weighted images. FLAIR images have been reported to enhance the diagnostic sensitivity for epileptogenic lesions such as hippocampal sclerosis and cortical dysplasia. For detecting hippocampal sclerosis, cross-sectional images perpendicular and parallel to the long axis of the hippocampus are needed [5]. Also, 3 Tesla MRI is useful when evaluating the indication for epilepsy surgery [6]. It is reported that 3 Tesla MRI depicts some lesions, such as hippocampal sclerosis, cortical dysplasia, and dysembryoplastic neuroepithelial tumor (DNT), which are not detected by 1.5 Tesla MRI [6].

■ References

1) Krumholz A, Wiebe S, Gronseth G, et al. Practice parameter: Evaluating an apparent unprovoked first seizure in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2007; 69(21): 1996-2007.
2) Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014; 55(4): 475-482.
3) Whiting P, Gupta R, Burch J, et al. A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery. Health Technol Assess. 2006; 10(4): 1-250, iii-iv.
4) Harden CL, Huff JS, Schwartz TH, et al. Reassessment: Neuroimaging in the emergency patient presenting with seizure (an evidence-based review) Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2007; 69(18): 1772-1780.
5) Morioka T, Nishio T, Mihara F, et al. Efficacy of the fluid attenuated inversion recovery (FLAIR) sequence of MRI as a preoperative diagnosis of hippocampal sclerosis. Neurol Surg. 1998; 26(2): 143-150. (in Japanese with English abstract)
6) Winston GP, Micallef C, Kendell BE, et al. The value of repeat neuroimaging for epilepsy at a tertiary referral centre: 16 years of experience. Epilepsy Res. 2013; 105(3): 349-355.

■ Search formula and secondary reference sources

PubMed search: October 30, 2008
((epileptic seizures OR epilepsy) AND ("Magnetic Resonance Imaging" [Mesh] OR "Tomography, X-Ray Computed" [Mesh])) AND ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio* OR practice guideline [pt] OR likelihood functions [mh] AND meta-analysis [mh] OR meta-analysis [pt] OR metaanaly* [tiab] OR "meta analysis" OR multicenter study [pt] OR validation studies [pt] OR systematic review* OR systematic [sb]) = 126

No references that could serve as evidence were found in Ichushi Web.

Additional PubMed search: July 2, 2015
("epilepsy/diagnosis" [MeSH Major Topic]) AND (("magnetic resonance imaging" [MeSH Terms] OR "ultrasonography" [MeSH Terms])) Filters: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 48

No references that could serve as evidence were found in Ichushi Web.

CQ 2-5

What are the useful functional neuroimaging studies for presurgical evaluation of epilepsy?

Summary

Nuclear medicine imaging techniques [interictal glucose metabolism fluorodeoxyglucose-positron emission tomography (FDG-PET), cerebral blood flow single photon emission computed tomography (SPECT), and iomazenil SPECT, as well as ictal cerebral blood flow SPECT] and magnetoencephalography (MEG) may be useful as presurgical evaluation tools for partial epilepsy by providing localization of MRI-negative epileptogenic zones.

Comment

In the presurgical evaluation of surgical indication for patients with partial epilepsy, nuclear medicine neuroimaging studies as well as magnetoencephalography (MEG) are used to localize the epileptogenic zones. Although the usefulness of these modalities in preoperative diagnosis is yet to be established [1], they may be useful in localizing MRI-negative epileptogenic zones. Even for MRI-positive lesions (with MRI structural lesions), additional information may be obtained.

Nuclear medicine imaging techniques include positron emission tomography (PET) and single photon emission computed tomography (SPECT). In general, epileptogenic zones exhibit reduced metabolism or blood flow during the interictal period, and increased metabolism or blood flow during the ictal period. The above examinations are conducted to image these changes in an attempt to identify the epileptogenic zone. PET methods include FDG-PET using [^{18}F] fluorodeoxyglucose (FDG) to observe glucose metabolism, and SPECT methods include cerebral blood flow SPECT using N-isopropyl-^{123}I-p-iodoamphetamine (IMP) or ^{99m}Tc-ethyl-cysteinate dimer (ECD) to measure cerebral blood flow.

The spatial resolution of FDG-PET is higher than that of SPECT, and the detection power of epileptogenic zone is also higher. Hence, FDG-PET may be useful for the detection of MRI-negative epileptogenic zone [2]. Especially, coregistering FDG-PET image to MRI enables us to know the accurate distribution of the regions with reduced metabolism. On the other hand, while many reports have indicated that ictal SPECT, which captures the high blood flow region at the time of seizure, is the most powerful method to detect the responsible focus, there is no clear evidence to support it [2]. Another powerful method is the subtraction ictal SPECT coregistered to MRI (SISCOM). In this method, the regions of statistically increased blood flow obtained by subtracting the interictal SPECT image from the ictal SPECT image are superimposed on MRI. This method is useful for detecting the epileptogenic zone in extra-temporal lobe epilepsy or MRI-negative partial epilepsy [3, 4].

Iomazenil SPECT using ^{123}I-iomazenil depicts the distribution of central benzodiazepine receptors (BZR). Central BZR couples with the $GABA_A$ receptor (the primary inhibitory neurotransmitters) to form the chloride channel. These inhibitory neurotransmitters are presumably decreased in the epileptogenic zone. Thus, iomazenil SPECT was anticipated to be capable of directly depicting their distribution. However, there is no clear evidence for its usefulness [5].

MEG is a neuromagnetic technique that measures the magnetic field generated by electrical activity of neurons. This method estimates the location of electrical source of interictal epileptic discharges. Magnetic source imaging is the technique of superimposing this electrical source on anatomical MRI. This method is a useful tool for noninvasive presurgical evaluation of epilepsy surgery [6]. When all noninvasive presurgical examinations fail to pinpoint the location of the epileptogenic zone, we should perform invasive EEG recording using subdural electrodes. In that case, magnetic source imaging provides useful information for deciding the sites of electrode placement. Use of magnetic source imaging in presurgical epilepsy evaluation has been found to correlate significantly with postoperative seizure-free outcome [7, 8].

References

1) Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol. 2014; 13(11): 1114-1126.
2) Whiting P, Gupta R, Burch J, et al. A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery. Health Technol Assess. 2006; 10(4): 1-250, iii-iv.
3) Matsuda H, Matsuda K, Nakamura F, et al. Contribution of subtraction ictal SPECT coregistered to MRI to epilepsy surgery: a multicenter study. Ann Nucl Med. 2009; 23(3): 283-291.
4) Von Oertzen TJ, Mormann F, Urbach H, et al. Prospective use of subtraction ictal SPECT coregistered to MRI (SISCOM) in presurgical evaluation of epilepsy. Epilepsia. 2011; 52(12): 2239-2248.
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6) Lau M, Yam D, Burneo JG. A systemic review on MEG and its use in the presurgical evaluation of localization-related epilepsy. Epilepsy Res. 2008; 79(2-3): 97-104.
7) Knowlton RC, Razdan SN, Limdi N, et al. Effect of epilepsy magnetic source imaging on intracranial electrode placement. Ann Neurol. 2009; 65(6): 716-723.
8) De Tiège X, Carrette E, Legros B, et al. Clinical added value of magnetic source imaging in the presurgical evaluation of refractory focal epilepsy. J Neurol Neurosurg Psychiatry. 2012; 83(4): 417-423.

Search formula and secondary reference sources

PubMed search: October 9, 2008

#1 ((epilepsy [majr] AND electroencephalography [majr] OR "brain wave" OR "brain waves" AND Magnetoencephalography [majr])) AND (meta-analysis [mh] OR meta-analysis [pt] OR metaanaly* [tiab] OR "meta analysis" OR multicenter study [pt] OR evaluation studies [pt] OR validation studies [pt] OR systematic review* OR systematic [sb] OR "sensitivity and specificity" [mh] OR diagnostic errors [mh] OR sensitivity [tiab] OR specificity [tiab] OR predictive value* OR likelihood ratio* OR false negative* OR false positive* OR controlled clinical trial [pt] OR randomized controlled trial [pt] OR double blind method [mh] OR single blind method [mh] OR practice guideline [pt] OR diagnosis, differential [mh] OR consensus development conference [pt] OR random* [tiab] OR random allocation [mh] OR single blind* [tiab] OR double blind* [tiab] OR triple blind* [tiab] OR likelihood functions [mh] OR area under curve [mh] OR reproducibility of results [mh]) = 25

#2 (epilepsy AND FDG-PET) AND ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio* OR practice guideline [pt] OR likelihood functions [mh]) = 117

#3 (epilepsy AND ("tomography, emission-computed, single-photon" [MeSH Terms] OR("tomography" [All Fields] AND "emission-computed" [All Fields] AND "single-photon" [All Fields]) OR "single-photon emission-computed tomography" [All Fields] OR "spect" [All Fields] OR "SPECT" [All Fields])) AND ("sensitivity and specificity" [mh] OR sensitivity [tiab] OR specificity [tiab] OR likelihood ratio* OR practice guideline [pt] OR likelihood functions [mh]) = 153

No references that could serve as evidence were found in Ichushi Web.

Additional PubMed search: July 2, 2015

("epilepsy/diagnosis" [MeSH Major Topic]) AND ((((Magnetoencephalography [MH]) OR "FDG-PET") OR (("SPECT" OR "Tomography, Emission-Computed, Single-Photon" [MeSH])))) OR ("PET" OR "Positron-Emission Tomography")) Filters: Clinical Trial; Meta-Analysis; Randomized Controlled Trial; Guideline; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 26

No references that could serve as evidence were found in Ichushi Web.