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Syndromic Diagnosis at the Epilepsy Clinic: Role of MRI in Lobar Epilepsies

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Summary: *Purpose:* Magnetic resonance imaging (MRI) is an essential diagnostic tool for the management of epilepsy at modern epilepsy clinics. This study was conducted to incorporate MRI features into the international classification of epilepsies and epilepsy syndromes (ICEES) proposed by the International League Against Epilepsy (ILAE).

Methods: Three hundred consecutive patients newly registered in the Yonsei Epilepsy Clinic underwent stepwise classifications based on clinical features, clinical EEG, and clinical EEG–MRI correlations. The patients were required to have epilepsy and have undergone both EEG and MRI for inclusion in the study. Interictal epileptiform discharges (IEDs) in the EEG were divided into lobar, multilobar, and generalized. MRI lesions were divided into lobar and multilobar lesions. Lobar epilepsies (LEs) were divided into temporal, frontal, parietal, occipital, rolandic, temporoparietooccipital junctional, multilobar, and nonlocalized LEs.

Results: Two hundred forty-nine patients satisfied the inclusion criteria. In the first-step diagnosis, 190 patients were classified as having localization-related epilepsy; 24 patients, generalized epilepsy; 34 patients, undetermined epilepsy; and one patient, a special syndrome. EEG revealed IEDs in 124 (50%) patients, and the second-step diagnosis changed the diagnostic categories of 79 (32%) patients. MRI detected lesions in 106 (43%) patients, and the third-step diagnosis changed the diagnostic categories of 30 (12%) patients. The nonspecific diagnostic categories of ICEES decreased from 49% to 37% and then to 29%, as diagnosis progressed from steps one to three. In cases of LE, MRI was superior to EEG in its clinical correlation. Additionally, the diagnostic precision in temporal lobe epilepsy was far better than that for other LEs.

Conclusions: The impact of MRI on ICEES was only modest in terms of changing diagnostic categories, although MRI provided a structural substrate for epilepsy in 38% of patients with negative EEGs. In LE, MRI was as sensitive as EEG, and its clinical correlation was superior to that of EEG, which strongly supports the rationale of incorporating MRI into ICEES. **Key Words:** Epileptic syndrome—Lobar epilepsy—Clinical-EEG correlation—Clinical-MRI correlation—EEG-MRI correlation.

As the concept of epilepsy management has become broader and more refined, the syndromic diagnosis of epilepsies has become a routine exercise in daily clinical practice. The international classification of epilepsies and epileptic syndromes (ICEES), proposed in 1985 and revised in 1989 by the International League Against Epilepsy (ILAE) (1,2), is the standard classification system adopted by most epilepsy communities worldwide.

The clinical application of ICEES had been tested by many investigators (3–15), and a majority of them approved its usefulness by demonstrating that they could classify almost all of their patients into the diagnostic categories of ICEES. Berg et al. (13) also reported a good interrater agreement. However, it should be pointed out that ICEES has many nonspecific diagnostic categories (i.e., cryptogenic localization-related epilepsies, other generalized epilepsies, or undetermined epilepsies) that may not define the epilepsy in any greater detail (7,16). These shortcomings of the ICEES classification system are more pronounced in lobar epilepsies (LEs), composing a vast majority of adult epilepsies. The syndromic classfication of LE in ICEES is based on the site of origin as documented by comprehensive clinical and laboratory investigations including video-EEG and intracranial EEG recordings, which are not readily applicable to most patients managed in outpatient clinics. Therefore syndromic classification beyond the level of assignment into symptomatic or cryptogenic LE has seldom been attempted in previous investigations. Additionally, Manford et al. (7) pointed to a high rate of discordance

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between clinical and EEG or computed tomography (CT) features for the topographic diagnosis of LE.

The limitation of ICEES in regards to the classification of LE has been a serious handicap to its clinical application because LE composes a major proportion of drug-resistant epilepsies, and its correct diagnosis and classification are quite crucial for the planning of future management. Over the past decade, magnetic resonance imaging (MRI) has exerted a great impact on the practice of epilepsy management. MRI may detect lesions in 50% to 74% of patients with LE attending an epilepsy clinic (17,18), and the presence of lesions in MRI may provide reliable evidence of seizure origin as well as other important clinical information such as etiology, surgical accessibility and outcome, prognosis, or responses to drug therapy (19–29). However, no attempt to incorporate MRI features into the current ICEES has yet been systematically undertaken. We were interested in investigating the possible role of MRI in the process of classifying epilepsies under the basic framework of ICEES.

METHODS

The registry forms of 300 consecutive new patients at the Yonsei Epilepsy Clinic (YEC) registering after January 1, 1997, were reviewed. The Yonsei Epilepsy Registry database contains complete clinical information on the patient's demography, past and developmental histories, family history, neurologic examination, description of seizures and their frequencies, precipitating factors, seizure occurrences related to circadian rhythms, age at seizure onset, previous drug therapy, clinical courses, and results of laboratory investigations [i.e., complete blood count (CBC), blood chemistry, urinalysis, EEG, and MRI]. Patients with a definitive diagnosis of epilepsy (two or more spontaneous seizures), and who had both EEG and MRI were included to the study. The algorithm of syndromic diagnosis consisted of three steps: (a) first-step diagnosis by clinical information; (b) second-step diagnosis by clinical–EEG correlation; and (c) third-step diagnosis by clinical–EEG–MRI correlations.

First-step diagnosis (clinical diagnosis)

Patient registry forms containing only clinical information were reviewed by three investigators (B.I.L., J.S.K., K.H.) together to develop the syndromic diagnosis in a consensus approach. The process of syndromic diagnosis followed the guidelines of ICEES, consisting of three hierarchical levels (13). At the first level, a syndrome is designated as localization-related epilepsy (LRE), generalized epilepsy (GE), or undetermined epilepsy (UDE). At the second level, an etiologic classification of idiopathic, symptomatic, or cryptogenic epilepsy is assigned for LRE and GE, whereas UDE is divided into those that have both focal and generalized features and those that do not have unequivocally focal or generalized features. Finally, at the third level, a specific syndrome is assigned to the individual patient. The third-level diagnosis of LE in this study included the following six major cortical regions: temporal lobe, frontal lobe, parietal lobe, occipital lobe, rolandic cortex, and the temporoparietooccipital (TPO) junctional region (Table 1). We treated third-level diagnoses having no clear definition in ICEES as nonspecific diagnostic categories, which included nonlocalized LE, nonspecific idiopathic GE, symptomatic GE of nonspecific etiology, and UDE.

Second-step diagnosis (clinical–EEG correlation)

All patients included in the study underwent 21-channel scalp EEG recording after overnight sleep deprivation. Surface electrodes were applied by using the international 10-20 system. Both anterior temporal electrodes (T_1 and T_2) and nasopharyngeal electrodes (Pg1 and Pg2) were routinely used bilaterally. EEG was re-

TABLE 1. *Guidelines for clinical diagnosis (first-step diagnosis) of lobar epilepsies*

Lobar epilepsies	Descriptions of seizures	
	Aura	Ictus
Temporal lobe	Visceral, experiential, emotional, psychic, or olfactory symptoms	Oroalimentary automatisms
	Nonspecific or none	Blank staring + oroalimentary automatisms
Frontal lobe	Visceral, emotional, psychic, or experiential symptoms	Blank staring only or asymmetric tonic spasm or hyperkinetic automatisms
	Nonspecific or none	Conscious head *version* or asymmetric tonic spasm
Parietal lobe	Vertigo or other symptoms of spatial distortions	Any ictal symptoms
Occipital lobe	Elementary visual symptoms, conscious eye-pulling sensation	Any ictal symptoms
Rolandic cortex	None	Elementary focal or lateralized somatosensory and/or motor symptoms
Temporo–parieto–occipital junction	Complex visual symptoms, mixtures of auras indicating parietal, occipital, or temporal lobe origin	Any ictal symptoms
Unlocalized	Nonspecific or mixture of auras indicating multiple lobar origin, or none	Presence of any partial features

corded for 60 min by using both monopolar and bipolar montages. For the purpose of this study, only interictal epileptiform discharges (IEDs) were considered positive findings. Using their topography, we classified the IEDs into lobar (maximal amplitude of IEDs at a single site or lobe), multilobar (IEDs involving two or more lobes), and generalized IEDs. Bilateral independent or synchronous IEDs involving the same lobe of both hemispheres were treated as lobar IEDs because the syndromic classification of LE in ICEES did not include a lateralization. Lobar IEDs were further divided into the six major regions according to the guidelines summarized in Table 2. The second-step diagnosis was based on the application of clinical–EEG correlations that were divided into concordant, discordant, and not discordant, as per the guidelines summarized in Table 2. If the clinical diagnosis was a specific syndrome, any EEG features known to occur in that syndrome were accepted as either concordant or not discordant (e.g., generalized SWC in primary reading epilepsy), and the clinical diagnosis was maintained. If the EEG disclosed specific patterns indicative of a specific syndrome, EEG diagnosis was respected for the second-step diagnosis [e.g., slow generalized SWC in clinically diagnosed LE → Lennox–Gastaut syndrome (LGS) instead of UDE]. In clinically diagnosed LE, a negative EEG was judged not discordant and the clinical diagnosis was kept; however, generalized IEDs were judged discordant, with the second-step diagnosis being changed to UDE. If the clinical diagnosis was localized lobar epilepsy (LLE), lobar IEDs in a different lobe were judged discordant, and the second-step diagnosis was unlocalized lobar epilepsy (ULE), whereas multilobar IEDs were judged not discordant, and the clinical diagnosis was maintained. In cases of clinically diagnosed ULE, multilobar IEDs were considered concordant, and the second-step diagnosis became multilobar epilepsy (MLE), whereas lobar IEDs were considered to be not discordant with the assignment of a second-step diagnosis into LLE, according to their topography. In clinically diagnosed GE, negative EEG and lobar or multilobar IEDs were considered discordant with the change of second-step diagnosis to UDE, LLE, or MLE, respectively. In clinically diagnosed UDE, the presence of lobar, multilobar, or generalized IEDs in the EEG was considered discordant to change in the second-step diagnosis to LLE, MLE or GE, respectively.

Third-step diagnosis (clinical–EEG–MRI correlation)

MRI was undertaken using a 1.5-T machine (GE Signa Hispeed, Milwaukee, WI, U.S.A.) according to the protocol consisting of transaxial T_1-weighted and T_2-weighted images, coronal T_2-weighted images perpendicular to the long axis of the temporal lobe, and coronal fluid-attenuated inversion recovery (FLAIR) images. The slice thickness of the transaxial and coronal images was 7 and 5 mm, respectively. MRIs were reviewed by two experienced neuroradiologists (D.I.K. and P.H.Y.), who divided the results into negative, lobar, and multilobar lesions, according to the distribution of lesions. Bilateral lesions involving the same lobe were treated as a lobar lesion, as was done for IEDs. For the incorporation of MRI lesions to ICEES, three independent correlations, clinical–EEG, EEG–MRI, and clinical–MRI correlations, were undertaken according to the basic principles applied for clinical–EEG correlations to determine their concordance, nondiscordance, and discordance (Table 2). The presence of MRI lesions was considered indicative of LE unless the second-step diagnosis was a specific syndrome known to have structural lesions (i.e., Lennox–Gastaut syndrome, Sturge–Weber syndrome). The guidelines of the third-step classification of LE in patients with positive findings in both EEG and

TABLE 2. *Guidelines for clinical–EEG and clinical–MRI correlations*

	Clinical–EEG (IEDs)			Clinical–MRI (lesions)		
Clinical Dx	C	ND	D	C	ND	D
Lobar epilepsy						
Temporal	$T_{1–2}$, $A_{1–2}$, $T_{3–4}$, $Pg_{1–2}$, ($F_{7–8}$)	N, ML, $T_{5–6}$	G, L: other lobe	L: limited to TL	N, ML	L: other lobe
Frontal	$Fp_{1–2}$, $F_{3–4}$, F_z, ($F_{7–8}$)	N, ML, $C_{3–4}$, C_z	G, L: other lobe	L: limited to FL	N, ML	L: other lobe
Paretal	$P_{3–4}$, P_z	N, ML, $C_{3–4}$, C_z	G, L: other lobe	L: limited to PL	N, ML	L: other lobe
Occipital	$O_{1–2}$	N, ML, $T_{5–6}$	G, L: other lobe	L: limited to OL	N, ML	L: other lobe
Rolandic	$C_{3–4}$, C_z	N, ML, $F_{3–4}$, F_z $P_{3–4}$, P_z	G, L: other lobe	L: limited to RC	N, ML, L: limited to adjacent FL or PL	L: other lobe
TPO junction	$T_{5–6}$	N, ML, $T_{3–4}$, $A_{1–2}$, $P_{3–4}$, $O_{1–2}$	G, L: other lobe	L: limited to TPO junction	N, ML, L: limited to adjacent TL, PL, or OL	L: other lobe
Unlocalized	ML	N, L	G	ML	N, L	—
GE						
Idiopathic	G	—	N, L, ML	—	N	L, ML
Crypt/symp	G	—	N, L, ML	—	N, L, ML	—
Symptomatic	G	—	N, L, ML	—	N, L, ML	—
UDE	—	N	L, ML, G	—	N	L, ML

C, concordant; ND, not discordant; D, discordant; N, negative; G, generalized; L, lobar; ML, multilobar; TL, temporal lobe; FL, frontal lobe; PL, parietal lobe; OL, occipital lobe; RC, rolandic cortex; TPO, temporoparietoccipital; $T_{1–2}$, anterior temporal electrodes; $Pg_{1–2}$, nasopharyngeal electrodes; ($F_{7–8}$), either frontal or temporal according to the topography of second maximum amplitude of IEDs; symptomatic, included the category of nonspecific etiologies.

MRI were based on a combination of three independent correlations as follows: (a) if there were one or more points of concordance among the three correlations, the third-step diagnosis followed the concordant correlation; (b) if there was no concordance among the three correlations, the presence of at least one discordant correlation made the third-step diagnosis ULE; and (c) if all three correlations were not discordant, the second-step diagnosis was maintained for the third-step diagnosis.

Statistics

We used a χ^2 test for the comparison of concordance or discordance rates of the clinical–EEG, clinical–MRI, and EEG–MRI correlations. To compare the diagnostic accuracies of each correlation, we used the term corrected concordance rate (CCR), which represented the difference between the concordance rate and the discordance rate [corrected concordance rate (CCR) = concordance rate (Pc) – discordance rate (Pd)], instead of κ, because each set of correlations contained a category of not discordant, comprising a relatively large proportion. The variance of CCR was defined by

$$\mathrm{Var(CCR)} = \mathrm{Pc}(1 - \mathrm{Pc})/n + \mathrm{PD}(1 - \mathrm{PD})/n + 2\mathrm{Pc} \cdot \mathrm{Pd}/n \quad (22)$$

Comparisons and 95% confidence intervals of CCR were performed by using the Z-test based on normal distribution. For example, the equation of the Z-test to compare the diagnostic accuracies of the clinical–EEG and clinical–MRI correlations is

$$Z = \frac{(\mathrm{CCR}\ \textit{clinical–EEG}) + (\mathrm{CCR}\ \textit{clinical–MRI})}{\sqrt{\mathrm{Var}\ (\mathrm{CCR}\ \textit{clinical–EEG}) + \mathrm{Var}\ (\mathrm{CCR}\ \textit{clinical–MRI})}}$$

or

$$Z = \frac{(\mathrm{CCR}\ \textit{clinical–EEG}–\mathrm{CCR}\ \textit{clinical–MRI})\ /}{\sqrt{\mathrm{Var}\ (\mathrm{CCR}\ \textit{clinical–EEG}) + \mathrm{Var}\ (\mathrm{CCR}\ \textit{clinical–MRI})}}$$

A two-tailed p value of ≤ 0.05 was taken to indicate significance.

RESULTS

Among 300 patients consecutively registered to the YEC, 51 patients were excluded from the study for the following reasons: 21 patients did not have epilepsy, 12 patients had a single seizure, and 16 patients had epilepsy but did not undergo either EEG or MRI. Thus the exercise of syndromic diagnosis was conducted with 249 patients. The patient set's demographic data revealed that the mean age was 25 ± 11.4 years, the mean duration of epilepsy was 9.8 ± 8.4 years, 129 patients were male, and 38 patients were either newly diagnosed or had previously untreated epilepsy. The results of the syndromic diagnosis at each step is summarized in Table 3.

First-step diagnosis (clinical diagnosis)

The syndromic diagnosis based on the clinical analysis of 249 patients disclosed that 190 (76%) patients had LRE, 24 (10%) patients had GE, and 34 (14%) patients had UDE. One patient developed recurrent seizures only after alcohol consumption and was classified as a special syndrome. Among the 190 patents classified into LRE, only one patient had idiopathic LRE (primary reading epilepsy), 56 patients had symptomatic LRE, and the remaining 133 patients had cryptogenic LRE. Two patients, one each from the symptomatic and the cryptogenic LRE demonstrated somatosensory-evoked seizures and were assigned to the category of "seizures with specific mode of precipitation (SSMP)." Thus 187 of 190 patients with LRE had LE, which included LLE in 106 patients and ULE in 81 patients. Twenty-four patients were diagnosed as GE, idiopathic in 14 patients, cryptogenic/symptomatic in seven patients, and symptomatic in three patients. Among these, 17 patients were assigned to specific syndromes, and seven patients were assigned to nonspecific categories. Thirty-four patients were categorized as UDE. Eight patients had both focal and generalized features, but none of them displayed clinical characteristics of specific syndromes. Twenty-six patients had either nocturnal grand mal seizures or poorly defined seizure phenomenology; thus they were assigned to the category of "without unequivocal evidence of focal or generalized epilepsies." Therefore the syndromic diagnosis based on clinical information assigned 127 (51%) patients to specific categories and 122 (49%) patients to nonspecific categories.

Second-step diagnosis (clinical–EEG correlations)

EEG revealed IEDs in 124 (50%) of 249 patients (Table 4). Among the 190 patients classified as LRE by clinical diagnosis, 89 (47%) patients had IEDs: lobar in 62 patients, multilobar in 19 patients, and generalized in eight patients. Among the 106 patients with a clinical diagnosis of LLE, 40 (38%) patients had lobar IEDs; clinical–EEG correlations were concordant in 23 patients, not discordant in four patients, and discordant in 13 patients, who were subsequently changed to ULE. Nine patients had multilobar IEDs, which were not discordant, and their first-step diagnoses were maintained. Thirty-two of the 81 patients with clinically diagnosed ULE had lobar or multilobar IEDs, and the second-step diagnosis was changed to LLE in 22 patients and MLE in 10 patients. Generalized IEDs were found in eight patients with LRE, which was considered not discordant in one patient with primary reading epilepsy and discordant in seven patients with LE. Their second-step diagnoses

TABLE 3. *Results of the stepwise classification of epileptic syndromes*

	Clinical	Clin–EEG	Clin–EEG–MRI
1. LRE	190 (76%)	199 (80%)	208 (84%)
1.1. Idiopathic			
1.1.1. Benign epilepsy of centrotemporal spikes	0	3 (3)	3
1.1.3. Primary reading epilepsy	1	1	1
1.2 Symptomatic			
1.2.2. Sensory evoked	1	1	1
1.2.3. Lobar epilepsy			
1.2.3.1. Localized	28	34 (13)	40 (8)
Temporal lobe	6	14 (8)	14 (1)
Frontal lobe	4	8 (5)	12 (4)
Parietal lobe	3	2	4 (2)
Occipital lobe	2	1	0
Rolandic area	10	8	8
TPO junction	3	1	2 (1)
1.2.3.2. Unlocalized[a]	27	18 (5)	9 (2)
1.2.3.3. Multilobar	0	5 (5)	11 (6)
1.3 Cryptogenic			
1.3.2. Sensory evoked	1	1	1
1.3.3. Lobar epilepsy			
1.3.3.1. Localized	78	86 (20)	91 (8)
Temporal lobe	27	36 (9)	37 (3)
Frontal lobe	10	16 (8)	20 (4)
Parietal lobe	9	7 (1)	8 (1)
Occipital lobe	9	7 (1)	7
Rolandic area	14	12	12
TPO junction	9	8 (1)	7
1.3.3.2. Unlocalized[a]	54	43 (8)	41 (3)
1.3.3.3. Multilobar	0	7 (7)	10 (3)
2. GE	24 (10%)	20 (8%)	20 (8%)
2.1. Idiopathic (58%)			
2.1.4. Childhood absence epilepsy	2	1	1
2.1.5. Juvenile absence epilepsy	1	2 (1)	2
2.1.6. Juvenile myoclonic epilepsy	4	4 (1)	4
2.1.7. GTC at awakening	10	1 (1)	1
2.1.8. GEF	1	1	1
2.1.9. Nonspecific (GTC only)[a]	6	1 (1)	1
2.2 Crypt/sympt (29%)			
2.2.2. Lennox–Gastaut syndrome	6	6 (2)	6
2.2.3. Myoclonic astatic epilepsy	1	1	1
2.3. Symptomatic (13%)			
2.3.1. Nonspecific etiology[a]	1	1 (1)	1
2.3.2. Specific diseases	2	2	2
3. UDE[a]	34 (14%)	29 (12%)	20 (8%)
3.1. Both F and G (24%)			
3.1.5. Others	8	10 (6)	7
3.2. Without unequivocal F or G (76%)	26	19 (5)	13
4. S.S	1 (0.4%)	1 (0.4%)	1 (0.4%)
4.1.3. Alcohol related	1	1	1
Total	249	249 (79)	249 (30)

LRE, localization-related epilepsy; GE, generalized epilepsy; UDE, undetermined epilepsy; SS, special syndrome; ( ), number of patients whose diagnostic categories changed; TPO, temporoparietooccipital; GEF, generalized epilepsy with fever.

[a] Nonspecific categories.

was changed to UDE with both focal and generalized features in six patients and LGS in one patient who demonstrated slow generalized SWC.

Among the 24 patients with a clinical diagnosis of GE, 12 patients revealed generalized IEDs, seven patients had lobar or multilobar IEDs, and five patients had no IEDs. Seven patients with lobar or multilobar IEDs were assigned to LE, and five patients with negative EEG were classified as UDE without unequivocal evidence of focal or generalized features. The EEGs of 34 patients with a clinical diagnosis of UDE revealed lobar or multilobar IEDs in 10 patients, with three of these showing characteristic EEG features of benign epilepsy with centrotemporal spikes (BECTS) and generalized IEDs in six patients, who were then classified according to their EEG features.

In summary, 43 (35%) of 124 patients with positive IEDs had discordant correlations, and 79 (32%) patients had changed their clinical diagnosis. Fifty-six (46%) of 122 patients with a clinical diagnosis of nonspecific cat-

TABLE 4. *Clinical–EEG, clinical–MRI, and EEG–MRI correlations in patients with clinically diagnosed lobar epilepsies*

	Clin–EEG			Clin–MRI			EEG–MRI[a]			Z-test (p value)		
Clinical diagnosis	n	C (%)	D (%)	n	C (%)	D %)	n	C (%)	D (%)	Clin–EEG vs. Clin–MRI	Clin–EEG vs. EEG–MRI	Clin–MRI vs. EEG–MRI
LE-1	88	33 (38)	20 (23)	91	48 (53)	6 (7)	54	29 (54)	6 (11)	0.003	0.02	0.75
LE-2	54	21 (39)	9 (17)	54	28 (52)	4 (7)	54	29 (54)	6 (11)	0.09	0.13	0.88
LLE-1	55	23 (42)	19 (35)	59	32 (54)	6 (10)	35	18 (51)	5 (14)	0.01	0.08	0.64
LLE-2	35	15 (43)	9 (26)	35	18 (51)	4 (11)	35	18 (51)	5 (14)	0.20	0.28	0.86
TLE	18	16 (89)	0	24	19 (79)	1 (5)	14	12 (86)	0	0.28	0.79	0.45
Ex-TLE	37	7 (19)	19 (51)	35	13 (37)	5 (14)	21	6 (29)	5 (24)	0.001	0.07	0.35
ULE	33	10 (30)	1 (3)	32	16 (50)	0	19	11 (58)	1 (5)	0.07	0.12	0.87

LE-1, all lobar epilepsy (187 patients); LE-2, all lobar epilepsy with positive EEG and MRI (54 patients); LLE-1, localized lobar epilepsy (106 patients); LLE-2, localized lobar epilepsy with positive EEG and MRI (35 patients); TLE, temporal lobe epilepsy (35 patients); Ex-TLE, extratemporal lobe epilepsy (73 patients); C, concordance; D, discordance; n, number of patients.

[a] EEG–MRI correlations in patients with positive EEG and MRI.

egories moved to specific categories, whereas 26 (20%) of 127 patients with a clinical diagnosis of specific categories moved to nonspecific categories, resulting in the reduction of the patients assigned to nonspecific diagnostic categories from 49% to 37%.

Third-step diagnosis (clinical, EEG, and MRI correlations)

MRI revealed structural lesions in 106 (43%) of 249 patients, including destructive lesions (encephalomalacia or focal atrophy) in 44 patients, hippocampal sclerosis in 25 patients, developmental lesions in 16 patients, mass lesions in 10 patients, infections or inflammatory lesions in five patients, and dual lesions in six patients. The distribution of lesions was lobar in 65 patients and multilobar in 41 patients.

MRI lesions were found in 47 (38%) of 125 patients with negative EEGs and in 59 (48%) of 124 patients with positive IEDs. Therefore both EEG and MRI results were negative in 78 (31%) patients and positive in 59 (24%) patients (Table 4). The incidence of MRI lesions in different syndromes of the second-step diagnosis were 47% in LRE, 6% in GE, and 31% in UDE.

Among the 199 patients with a second-step diagnosis of LRE, MRI changed the diagnostic categories in 21 patients from LLE (including MLE) to ULE in five patients and from ULE to LLE in 16 patients. Three of 20 patients with GE had MRI lesions that were not discordant in one patient with LGS and concordant in two patients with tuberous sclerosis and Sturge–Weber syndrome, respectively. Thus MRI did not change the diagnosis in any patient with a second-step diagnosis of GE. Among the 29 patients with UDE, MRI detected lesions in nine patients with subsequent changes of diagnosis into LE. Therefore, the incorporation of MRI into ICEES changed the diagnostic categories in a total of 30 (12%) patients and decreased the proportion of patients assigned to nonspecific diagnostic categories from 37% to 29%.

Clinical–EEG–MRI correlations in clinically diagnosed lobar epilepsy

Considering that MRI lesions represent the structural substrate for LE, it was deemed important to compare the degree of three independent correlations (clinical–EEG, clinical–MRI, and EEG–MRI correlations) in this group of patients separately (Table 4). Among the 187 patients assigned to LE clinically, clinical–MRI and EEG–MRI correlations revealed higher concordance rates and lower discordance rates than did clinical–EEG correlations. The Z-test analysis revealed significantly better diagnostic accuracies of clinical–MRI and EEG–MRI correlations than did clinical–EEG correlation ($p = 0.003$ and $p = 0.02$, respectively). If we restricted the analysis to the 54 patients with positive EEG and MRI, the diagnostic accuracy of the clinical–MRI correlation was slightly superior to that of the clinical–EEG correlation ($p = 0.09$ by Z-test) without any differences between the EEG–MRI and clinical–EEG correlations ($p = 0.13$ by z-test). A similar analysis was conducted in patients with clinically diagnosed LLE because the inclusion of ULE may present some theoretic problems because of its clinical uncertainties. The concordance rates of clinical–EEG (55 patients) and clinical–MRI (59 patients) correlations were 42% and 54%, respectively ($p = 0.2$ by χ^2 test), whereas their discordance rates were 35% and 10%, respectively ($p = 0.002$ by χ^2 test). The Z-test analysis demonstrated a better diagnostic accuracy of clinical–MRI correlation than the clinical–EEG correlation ($p = 0.01$).

In the next step, we divided the LLE into TLE and extra-TLE. The concordance rates of clinical–EEG, clinical–MRI, and EEG–MRI correlations in TLE were much higher than that of extra-TLE, and the comparisons of all three correlations between TLE and extra-TLE by Z-test were significantly different ($p \leq 0.002$), suggesting a much higher diagnostic precision for TLE than for extra-TLE. Conversely, EEG was not very useful in extra-TLE diagnosis, as the clinical–EEG correlation had

the lowest concordance rate and the highest discordance rate, with significantly better diagnostic accuracies for clinical–MRI ($p = 0.001$ by Z-test) versus the clinical–EEG correlation. Thus MRI appeared to be an invaluable addition to ICEES for the topographic diagnosis of extra-TLE. Further to evaluate the diagnostic precision of LE, we looked at the combinations of clinical–EEG, clinical–MRI, and EEG–MRI correlations in 54 patients with both positive results of EEG and MRI (Table 5). As expected, the diagnostic precision of TLE was excellent, as 79% of patients demonstrated complete concordance of the three correlations as compared with that of 10% in extra-TLE. These results suggest that the topographic diagnosis of extra-TLE carries a high chance of diagnostic error.

DISCUSSION

The basic concept of ICEES, clusters of signs and symptoms customarily occurring together, should be viewed as an intermediary step in the evolving process from seizure classification to etiologic classification. At present, MRI is considered the most important diagnostic tool for investigating the etiology of epilepsies in vivo and the terms, "lesional or nonlesional epilepsies," have become quite prevalent for the planning of epilepsy management and prediction of the prognosis of individual patients (16–21,23), resulting in the promotion of MRI as an essential procedure for patient evaluation in most modern epilepsy clinics. However, the current ICEES fails to include a guideline applying MRI features to its classification scheme, which is a serious criticism raised against ICEES (16,23). Therefore, efforts to reconcile MRI features to the framework of ICEES are crucial for improving its clinical utility.

In this study, we undertook a serial stepwise syndromic diagnosis according to a process of gathering informations, including the diagnosis based on the clinical information only, diagnosis based on the clinical–EEG correlation, and then the diagnosis based on clinical–EEG–MRI correlations. In this scheme, the diagnosis based on clinical–EEG correlations should be comparable to that of ICEES. EEG has been the most important diagnostic tool in epilepsy; however, it requires a careful clinical correlation for the correct diagnosis of epileptic syndromes. We applied the same principle for the incorporation of MRI to ICEES because any lesions on MRI required clinical or EEG correlation to prove their epileptogenicity. Thus the final classification after MRI was based on a combination of the clinical–EEG, clinical–MRI, and EEG–MRI correlations.

TABLE 5. *Combination of clinical–EEG, clinical–MRI, and EEG–MRI correlations in clinically diagnosed lobar epilepsies with positive results of EEG and MRI*

Combinations of correlations	Localized lobar epilepsy			Unlocalized lobar epilepsy	Total
	TLE	Ex-TLE	Subtotal		
C-C-C	11 (79%)	2 (10%)	13 (37%)	5 (26%)	18 (33%)
C-D/ND-D/ND	2 (14%)	10 (48%)	12 (34%)	12 (63%)	24 (44%)
ND-ND-ND	0	5 (24%)	5 (14%)	1 (5%)	6 (11%)
ND-D/ND-D/ND	1 (7%)	2 (10%)	3 (9%)	1 (5%)	4 (7%)
D-D-D	0	2 (10%)	2 (6%)	0	2 (4%)

C, concordance; ND, no discordance; D, discordance; TLE, temporal lobe epilepsy; Ex-TLE, extratemporal lobe epilepsy.

The overall results of the stepwise classification can be summarized as follows: EEG was positive in a half of the patients, changed the diagnostic categories in 79 (32%) patients, and decreased the proportion of nonspecific diagnostic categories from 49% to 37%, whereas the subsequent application of MRI to ICEES revealed lesions in 43%, changed the diagnostic categories in 30 (12%) patients, and decreased the nonspecific diagnostic categories from 37% to 29%. Thus the impact of MRI on the overall results of ICEES appeared to be modest. However, the fact that >80% of patients referred to the epilepsy clinic had LE and almost half of these had cerebral lesions may have an important clinical implication to support the rationale of adopting MRI as a routine investigational tool in the clinical setting. The high proportion of LE and a low proportion of GE in this study were apparently related to our clinical setting, heavily oriented toward adult patients with drug-resistant epilepsies. The number of patients diagnosed with GE decreased from 24 to 20 at the second step and did not change at all in the third-step diagnosis, which strongly supported the finding that ICEES is quite reliable and useful for the classification of GE. MRI revealed lesions in about a third of patients assigned to UDE by ICEES; thus its proportion was decreased from 12% at the second step to 8% at the final step.

Because it was expected that the major contribution of MRI to ICEES should be at the localization of seizure origin in LE, further data analysis was undertaken. The topographic diagnosis of LE in this study did not include ILAE sites but included the four major lobes, the rolandic cortex, and the TPO junctional cortex, because a further localization to ILAE sites usually required the use of intracranial electrodes. Rektor et al. (24) reported a good agreement between epileptologists with or without access to the intracranial EEG recordings for the localization of the epileptogenic region to major lobes, but a large discrepancy was observed in the localization to more restricted sites. The rolandic cortex was included because seizures originating from this region were readily identifiable clinically, and many patients reported both primary motor and somatosensory symptoms together. The TPO junctional cortex was included because of the difficulty of dividing this region into different major lobes. These two regions anatomically belong to the major lobes, and their topographical definition in terms of EEG and MRI features is not well established.

Thus we included focal features of EEG and MRI seen in the adjacent lobar regions as not discordant in patients with a clinical diagnosis of RE or TPOE.

In this study, 106 patents with clinically diagnosed LLE had characteristic clinical features suggesting their seizure origin from one of the major cortical regions. EEG was positive in 55 patents, MRI revealed lesions in 59 patents, and both tests were positive in 35 patients. The comparisons of diagnostic accuracies between clinical–EEG and clinical–MRI correlations in these patients revealed a significant superiority of MRI to EEG for the topographic diagnosis of LE. The subgroup analysis also clearly demonstrated the markedly different diagnostic precisions between TLE and extra-TLE. The concordance rates of clinical–EEG and clinical–MRI correlations were much higher and their discordant rates were much lower in TLE versus extra-TLE. In addition, the combination of correlations among three variables revealed a complete concordance rate of 79% in TLE but only 10% in extra-TLE. These results indicate that the diagnostic precision of TLE is far superior to that of extra-TLE, a result probably related to the well-defined clinical characteristics of TLE as compared with other LEs (25,26). Therefore the contribution of MRI to the syndromic diagnosis of TLE was rather limited. However, it should be stressed that MRI provided pathologic substrates in more than two thirds of patients or in more than half of the patients with negative EEGs, who were clinically diagnosed as TLE. Conversely, in cases of extra-TLE, the degree of clinical correlations was clearly better with MRI than EEG, and EEG–MRI correlation provided another basis for the syndromic diagnosis, also superior to the clinical–EEG correlation. Thus MRI seemed to be an invaluable addition to ICEES for the topographic diagnosis of extra-TLE, a finding in good agreement with the results of presurgical evaluations of intractable neocortical epilepsies (16,27,28). However, the topographic diagnosis of extra-TLE was still problematic, even with the incorporation of MRI, as evidenced by the absence of any concordance among the three correlations in 42% of patients and a <50% detection rate of lesions by MRI. We certainly agree to the proposal of a simpler classification of LE into TLE and extra-TLE at the level of the outpatient clinic (22).

We can conclude that the overall impact of MRI on the clinical application of ICEES at the epilepsy clinic is modest. However, MRI provides a structural substrate for epilepsy in 38% of patients with negative EEGs. Moreover, in patients with LE, MRI is as sensitive as EEG and correlates with clinical features better than EEG. These points strongly argue the importance of incorporating MRI into the current ICEES. The subgroup analysis revealed that the clinical–EEG–MRI correlation in TLE is very high; MRI contributed to a more specific diagnosis primarily in extra-TLE, and MRI was not generally needed if the diagnosis by clinical–EEG correlation was idiopathic GE or LRE. We propose that any future revision of ICEES should include a separate category of lesional epilepsies, a category composing >40% of patients attending epilepsy clinics.

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