Problems in the Application of the New International Classification of Epilepsy Proposed by ILAE

Seong Hyun Kim¹  Heung Dong Kim¹

Summary: Recent classification of epilepsy proposed by ILAE in 2001 contains diverse scientific observations to guide better approaches to epilepsy than prior one in 1989. But in clinical practice, there are significant discrepancies between etiologies (genetic defect, location of epileptic zone, etc) and clinical phenotypes (epilepsy types, AED responsiveness). There are still limitations for the classification to obtain essential diagnostic information from diagnostic modalities such as EEG and MRI, and many unknown determining factors influencing the onset of epileptic condition, clinical progress and evolution and prognosis.

This review is to provide current proposal and the direction of classification for better practical guide to epileptic patients.

Key Words: ILAE classification, epilepsy, epilepsy syndromes

Introduction

Recent classification of epilepsy proposed by ILAE in 2001 contains diverse scientific observations to guide better approaches to epilepsy than prior international classification in 1989. Ictal phenomenology, seizure type, syndrome, etiology, and impairment are 5 main axes of diagnostic schemes to facilitate the clinical approaches. Many new or changed concepts are also proposed to classification for better application.

In clinical practice, there are significant discrepancies among etiologies, epilepsy types, and pathogenetic mechanisms, between location of epileptogenic zone and clinical phenomenologies, between genetic defect and clinical phenotypic disease expression, and between syndromic diagnosis and AED responsiveness. We still do not know many of determining factors influencing the onset of epileptic condition, clinical progress and evolution, responsiveness to treatment, disease severity, and prognosis. There are still limitations to obtain essential diagnostic information from patients and/or diagnostic modalities including ictal/interictal EEG and MRI. These situations could limit this classification used for an exact practical guide to treat and expect outcome in all the individual patients.

Despite of the recent proposal for international classification of epilepsy by ILAE, significant pro-

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Table 1  Definitions of Key Terms – ILAE (2001)

- Epileptic seizure type: An ictal event believed to represent a unique pathophysiological mechanism and anatomical substrate. This is a diagnostic entity with etiological, therapeutic and prognostic implications (new concept)
- Epilepsy syndrome: A complex of signs and symptoms that define a unique epilepsy condition with different etiologies. This must involve more than just the seizure type; thus frontal lobe seizures per se, for instance, do not constitute a syndrome (changed concept)
- Epilepsy disease: A pathological condition with a single specific, well-defined etiology. Thus, progressive myoclonus epilepsy is a syndrome, but Unverricht–Lundborg is a disease (new concept)
- Epileptic encephalopathy: A condition in which the epileptic processes themselves are believed to contribute to the disturbance in cerebral function (new concept)
- Benign epilepsy syndrome: A syndrome characterized by epileptic seizures that are easily treated, or require no treatment and remit without sequelae (clarified concept)
- Reflex epilepsy syndrome: A syndrome in which all epileptic seizures are precipitated by sensory stimuli. Reflex seizures that occur in focal and generalized epilepsy syndromes that are also associated with spontaneous seizures are listed as seizure types. Isolated reflex seizures can also occur in situations that do not necessarily require a diagnosis of epilepsy. Seizures precipitated by other special circumstances, such as fever or alcohol withdrawal, are not reflex seizures (changed concept)
- Focal seizures and syndromes: Replaces the terms partial seizures and localization-related syndromes (changed terms)
- Simple and complex partial epileptic seizures: These terms are no longer recommended, nor will they be replaced. Ictal impairment of consciousness will be described when appropriate for individual seizures, but will not be used to classify specific seizure types (new concept)
- Idiopathic epilepsy syndromes: (unchanged term)
- Symptomatic epilepsy syndrome: (unchanged term)
- Probably symptomatic epilepsy syndrome: Synonymous with, but preferred to, the term cryptogenic, used to define syndromes that are believed to be symptomatic, but no etiology has been identified (new term)

portion of epilepsy still has difficulties in the classification of seizures and syndromes. We review the current status of classification and its limitation.

Introduction–history of epilepsy classification

The first ILAE epilepsy classification provided a worldwide commonly accepted standard classification system in 1970, which characterized as major dichotomy between generalized and focal epilepsies. It is based on clinical characteristics of each seizure type combined with electroencephalographic (EEG) features, etiology, and age at manifestation (Merlis, 1970).

Since the beginning, ILAE has changed the classification continuously to complement the prior one. The first revised ILAE classification introduced another etiological concept of classification (as idiopathic and symptomatic) and listed multiple syndromes defined as a cluster of semiological seizure types, EEG patterns etiologies, age at onset, and seizure frequency (1985). Four years later, the concept of cryptogenic was introduced to classify epilepsies which were presumed to be symptomatic, but without definite proof at present (1989). This syndrome-oriented approach to classify epilepsies is applied again to recent ILAE classification although this has been criticized and proposed for more clinically-oriented classification for its easier application[4-9].

The most current proposed classification by ILAE Task Force is based on epilepsy syndromes and presents a multi-axial approach (ILAE, 2001). It is over-focused on establishing criteria for identification of specific epileptic seizure types and specific epilepsy syndromes as unique diagnostic entities by evidence-based approach.

Recent report from ILAE task force also described that this proposal needs to be revised as scientific evidences for epilepsy keep in progress[9].
Table 2 Five Axes used in Proposed Diagnostic Scheme − ILAE (2001)

- Axis 1: Ictal phenomenology − from the Glossary of Descriptive Ictal Terminology, can be used to describe ictal events with any degree of detail needed.
- Axis 2: Seizure type: from the List of Epileptic Seizures. Localization within the brain and precipitating stimuli for reflex seizures should be specified when appropriate.
- Axis 3: Syndrome: from the List of Epilepsy Syndromes, with the understanding that a syndromic diagnosis may not always be possible.
- Axis 4: Etiology: from a Classification of Diseases Frequently Associated with Epileptic Seizures or Epilepsy Syndromes when possible, genetic defects, or specific pathological substrates for symptomatic focal epilepsies.
- Axis 5: Impairment: this optional, but often useful, additional diagnostic parameter can be derived from an impairment classification adapted from the WHO ICIDH−2.

We review the current status of the New ILAE classification (2001) and its limitation.

Recent ILAE classification (2001)

Key Terms from Proposed Diagnostic Scheme for Epileptic Seizures and with Epilepsy, ILAE (2001)

The ILAE Task Force described that the dichotomies of the 1989 epilepsy classification using localization related versus generalized, and idiopathic versus symptomatic, are too simplistic and often difficult to apply. Some revisions in the definitions of key terms have been proposed (Table 1), as well as a diagnostic scheme to be used to describe individual patients with epilepsy (Table 2) (Engel, 2001).

Axis 1 of the diagnostic scheme involves a detailed description of ictal phenomenology from the Glossary of Descriptive Ictal Terminology (Blume et al, 2001)

Axis 2 is diagnosis of specific seizure type(s). The concept of seizure type is a new concept (Engel, 2001), as a diagnostic entity, rather than a description of clinical behavior and EEG, in the current 1981 seizure classification. Axis 3 is diagnosis of a specific syndrome. Axis 5 is an optional assessment of impairment taken from the WHOICIDH−2 classification.

Epileptic seizure types

The ILAE has recently accepted the definition of an epileptic seizure as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain". There are many types of epileptic seizures. An epileptic seizure type that represents a unique diagnostic entity or natural class ought to be defined on the basis of a distinct pathophysiology and anatomical substrate.

The following criteria were used to select specific seizure types as possibly unique diagnostic entities, for further hypothesis testing.

- Pathophysiologic mechanisms: Including electrophysiological features, neural networks, neurotransmitter evidence if known.
- Neuronal substrates: Although the neocortex is considered as a single substrate regardless of exact location, other indispensable brain structures and networks for generating neuronal activity should be included (e. g., thalamic reticular nucleus).
- Response to anti-epileptic drugs (AEDs): Selective responsiveness to or exacerbation with specific drugs can suggest specific mechanism of seizure generation.
- Ictal EEG patterns: Specific ictal EEG patterns can be necessary diagnostic features of specific seizure types (e. g., 3/sec s/w for absences).
- Propagation patterns and postictal features: Patterns of propagation, or lack of propagation, and postictal features, or lack of them, help to define pathophysiologic mechanisms and anatomic substrates (e. g., typical absences have no postic-
<table>
<thead>
<tr>
<th>Table 3</th>
<th>Epileptic Seizure Types and Precipitating Stimuli for Reflex Seizures, ILAE (2001)</th>
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<tr>
<td><strong>-Self Limited Seizure Type</strong></td>
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<td><strong>Generalized seizures</strong></td>
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<tr>
<td>• Tonic–clonic seizures (includes variations beginning with a clonic or myoclonic phase)</td>
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<tr>
<td>• Clonic seizures</td>
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<td>\quad Without tonic features</td>
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<td>\quad With tonic features</td>
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<td>• Typical absence seizures</td>
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<td>• Atypical absence seizures</td>
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<td>• Myoclonic absence seizures</td>
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<td>• Tonic seizures</td>
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<td>• Spasms</td>
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<td>• Myoclonic seizures</td>
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<td>\quad Without absences</td>
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<td>\quad With absences</td>
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<td>• Myoclonic atonic seizures</td>
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<td>• Negative myoclonus</td>
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<tr>
<td>• Atonic seizures</td>
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<td><strong>Focal seizures</strong></td>
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<tr>
<td>• Focal sensory seizures</td>
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<td>\quad With elementary sensory symptoms (e.g., occipital and parietal lobe seizures)</td>
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<td>\quad With experiential sensory symptoms (e.g., temporo parieto occipital junction seizures)</td>
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<td>• Focal motor seizures</td>
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<td>\quad With elementary clonic motor signs</td>
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<td>\quad With asymmetrical tonic motor seizures (e.g., supplementary motor seizures)</td>
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<td>\quad With typical (temporal lobe) automatisms (e.g., mesial temporal lobe seizures)</td>
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<td>\quad With hyperkinetic automatisms</td>
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<td>\quad With focal negative myoclonus</td>
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<td>\quad With inhibitory motor seizures</td>
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<td>• Gelastic seizures</td>
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<td>• Hemiclonic seizures</td>
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<td>• Secondarily generalized seizures</td>
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<td><strong>-Continuous seizure types</strong></td>
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<td><strong>Generalized status epilepticus</strong></td>
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<td>• Generalized tonic–clonic status epilepticus</td>
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<td>• Clonic status epilepticus</td>
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<td>• Absence status epilepticus</td>
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<td>• Tonic status epilepticus</td>
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<td>• Myoclonic status epilepticus</td>
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<td><strong>Focal status epilepticus</strong></td>
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<tr>
<td>• Epilepsia partialis continua of Kojevnikov</td>
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<td>• Aura continua</td>
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<td>• Limbic status epilepticus (psychomotor status)</td>
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<td>• Hemiconvulsive status</td>
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<td><strong>-Precipitating Stimuli for Reflex Seizures</strong></td>
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<tr>
<td>• Visual stimuli</td>
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<td>\quad Flickering light: color to be specified when possible</td>
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<td>\quad Patterns</td>
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<td>\quad Other visual stimuli</td>
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<td>• Thinking</td>
<td></td>
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<td>• Music</td>
<td></td>
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<td>• Eating</td>
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<td>• Praxis</td>
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<td>• Somatosensory</td>
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<td>• Proprrioceptive</td>
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<td>• Reading</td>
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<td>• Hot water</td>
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<td>• Startle</td>
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**Table 4** Epilepsy Syndromes and Related Conditions - ILAE (2001)

- Benign familial neonatal seizures
- Early myoclonic encephalopathy
- Ohtahara syndrome
- Migrating partial seizures of infancy
- West syndrome
- Benign myoclonic epilepsy in infancy
- Benign familial infantile seizures
- Benign infantile seizures (non-familial)
- Dravet’s syndrome
- HHE syndrome
- Myoclonic status in non-progressive encephalopathies
- Benign childhood epilepsy with centrotemporal spikes
- Early onset benign childhood occipital epilepsy (Panayiotopoulos type)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Epilepsy with myoclonic-astatic seizures
- Lennox-Gastaut syndrome
- Landau-Kleffner syndrome
- Epilepsy with continuous spike-and-waves during slow-wave sleep (other than LKS)
- Childhood absence epilepsy
- Progressive myoclonus epilepsies
- Idiopathic generalized epilepsies with variable phenotypes
  - Juvenile absence epilepsy
  - Juvenile myoclonic epilepsy
  - Epilepsy with generalized tonic-clonic seizures only
- Reflex epilepsies
  - Idiopathic photosensitive occipital lobe epilepsy
  - Other visual sensitive epilepsies
  - Primary reading epilepsy
  - Startle epilepsy
- Autosomal dominant nocturnal frontal lobe epilepsy
- Familial temporal lobe epilepsies
- Generalized epilepsies with febrile seizures plus
- Familial focal epilepsy with variable foci
- Symptomatic (or probably symptomatic) focal epilepsies
  - Limbic epilepsies
    - Mesial temporal lobe epilepsy with hippocampal sclerosis
    - Mesial temporal lobe epilepsy defined by specific etiologies
    - Other types defined by location and etiology
  - Neocortical epilepsies
    - Rasmussen syndrome
    - Other types defined by location and etiology
- Conditions with epileptic seizures that do not require a diagnosis of epilepsy
  - Benign neonatal seizures
  - Febrile seizures
  - Reflex seizures
  - Alcohol-withdrawal seizures
  - Drug or other chemically induced seizures
  - Immediate and early post cerebral insult seizures
  - Single seizures or isolated clusters of seizures
  - Rarely repeated seizures (oligoepilepsy)
tal dysfunction; contralateral propagation is slow for hippocampal seizures vs. fast for neocortical seizures).

- Epilepsy syndrome (s): Syndrome that is associated with this seizure type.

Terminology of dichotomy classification as partial versus generalized seizure should be discarded because no seizures or syndromes are truly generalized nor any seizures or syndromes are solely due to a discretely focal epileptogenic process.

The Core Group recommended to give the terms “focal” and “generalized, with the understanding that the former does not necessarily imply that the epileptogenic region is limited to a small circumscribed area, nor does the latter imply that the entire brain is involved in initiation of the epileptogenic process.

Epileptic seizure types are shown in Table 3.

Epileptic Syndrome

An epilepsy syndrome is defined as “a complex of signs and symptoms that define a unique epileptic condition”. Task force added that “it must involve more than just a seizure type”, that is, it needs to contain not only predisposition to generate epileptic seizures but also by neurobiological, cognitive, psychological social consequences of the condition). It means epilepsy is distinguished from epileptic diseases, which were defined as “a pathologic condition with a single, specific, well-defined etiology”. The epilepsy syndromes were evaluated according to the following criteria such as epileptic seizure types, age of onset, progressive nature, interictal EEG, associated interictal signs and symptoms, pathophysiologic mechanisms, genetic basis. Epileptic syndromes are listed in Table 4.

Limitations of the 2001 ILAE proposal

As discussed before, it is focused on establishing criteria for identification of specific epileptic seizure types and specific epilepsy syndromes as unique diagnostic entities by evidence-based approach. But such a large numbers of more than 50 epilepsy syndromes make difficulties for most of clinicians to use and understand in their actual practice. Moreover, this ILAE epilepsy syndrome classification is not applicable to most patients with epilepsy, but only a limited number of patients. Some studies showed only 4% in adult and 21% in children could be diagnosed with a specific epilepsy syndrome of the ILAE classification. In another 100 consecutive patients, syndromes were probable in 19%, not defined as a syndrome in 32%. Overall, 5–30% of patients can be classified according to the ILAE syndromes. Current classification of epileptic syndromes provides limited reliability to the prognosis, outcomes, and etiology due to heterogeneity within each syndromes. Furthermore, syndromes can change with age, that means, the same patient can bear several epilepsy syndrome diagnosis at different ages. Finally, semiology, epileptic seizure type, epilepsy syndrome can be overlap.

Patient-oriented Approach

These limitations of the syndromic approach to epilepsy classification led to propose alternative concepts for more clinically oriented classification. A recently published study suggest trial to shift from syndrome oriented approach to patient oriented approach, using independent criteria in the following five dimensions.

- Dimension 1 Epileptogenic zone (epilepsy syndrome): 4 major terms used for indicating the epileptogenic zone, which is define as "the area of cortex, indispensable for the generation of epileptic seizure" as focal, multilobar, hemispheric, multifocal and generalized.

- Dimension 2 Semiologic seizure classification: it is based solely on seizure symptomatology, its main clinical features.

- Dimension 3 Etiology, multifaceted ap-
approach: this consists of 12 categories and subcategories.

- Dimension 4: Seizure frequency: it is categorized to provide a guideline for epilepsy severity in total seizure frequency during a given time.
- Dimension 5: Related medical condition: additional information in the history (example: head trauma with loss of consciousness), physical examination (example: left hemiparesis or mental retardation) and additional diagnostic tests (example: EEG findings)

These 5 dimensional classification systems are well defined in order to minimize overlap with minimal redundancy of information between independent dimensions.

In addition, following the general neurological principles, there is no need for knowledge about specific diagnostic tools such as MRI and/or EEG. It is very difficult for general physicians without EEG or even for the specialists without immediate EEG support to classify all the patients in effective manner.

In short, there are lots of advantages of five dimensional epilepsy classification such as independence of dimension, independence from contemporary diagnostic tools, applicability to all patients and it includes all essential information and follows general neurological principles. It also useful for research with scientific taxonomic accuracy and completeness.

**Limitations to reach perfect classification**

More than anything else, it is not fully understood that the determining factors influencing the onset of epileptic condition, clinical progress and evolution, responsiveness to treatment, disease severity, and prognosis.

Moreover, as discussed above, there are many discrepancies basically: etiologies vs. epilepsy types/pathogenetic mechanisms, location of epileptogenic zone vs. clinical phenomenologies, genetic defect vs. clinical phenotypic expression, syndromic diagnosis vs. AED responsiveness.

Besides, there are still technical limitations to obtain essential diagnostic information from patients and/or diagnostic modalities including ictal/interictal EEG and MRI.

**Conclusion**

Epilepsy classification is not finalized yet, and it should keep in revision for better patient-oriented approaches with continuously changing dynamic process by the additional information in etiology and epileptogenic process from the technical and research advances. Further research about genes plays a role to produce clinical phenotypes and spectrums. We should keep in mind that the goal of epilepsy classification is to provide exact practical guide to treat and expect outcome in every individual patients.

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