

Application of the 2001 diagnostic scheme and the 2006 ILAE report of seizure and epilepsy: a feedback from the clinical practice of adult epilepsy

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ABSTRACT – Purpose. To clarify the clinical validity and feasibility of the diagnostic scheme for seizures and epilepsy proposed by the International League Against Epilepsy (ILAE) in 2001 (the 2001 Scheme) and the report of the ILAE classification core group in 2006 (the 2006 Report). **Methods.** One hundred consecutive patients with epilepsy who visited the Neurology Clinic (Group 1) and 100 patients with intractable epilepsy who had undergone prolonged scalp video-EEG monitoring (Group 2) in Kyoto University Hospital were enrolled. The 2001 Scheme (Axis 1 to 4) and the 2006 Report (seizure types and epileptic syndromes) were applied to Group 1. Axis 1 was applied to Group 2 to evaluate the diversity of seizure semiology. **Results.** Group 1 demonstrated 145 seizures of different types (generalized tonic-clonic seizures: 23%, complex partial seizures (CPS): 29%, simple partial seizures: 21% and secondarily generalized tonic-clonic seizures: 21% according to the 1981 classification. In Axis 1 (ictal phenomenology) of the 2001 scheme, 184 and 333 items were listed in Groups 1 and 2, respectively, and seizure semiology was described independent of EEG findings. However, there was duplications or discordance among the items. In Axis 2 (seizure types) of Group 1, 62% and 26% of CPS were further labeled as focal motor or sensory seizures, respectively; the remainder (24%) did not meet inclusion criteria for any category. In Axis 3 (epilepsy syndromes), 94% of patients were sorted, and familial temporal lobe epilepsy was added. Axis 4 described detailed etiology. Application of seizure types of the 2006 Report required consideration of ictal phenomenology to determine spread patterns. Epileptic syndromes of the 2006 Report were assignable to 70% of patients. **Conclusions.** It is important to achieve intra- and inter-axial accordance for the establishment of a more practical diagnostic scheme, which may provide a more useful tool for the diagnosis of less obvious aspects of epilepsy.

Key words: epileptic seizures, epilepsy syndromes, the 2001 Scheme, the 2006 Report

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The abstract of this study was presented in workshops at the 39th and 41st Annual Meeting of the Japanese Epilepsy Society, Asahikawa in 2005, and Fukuoka in 2007, Japan, respectively and at the 6th Asian and Oceanian Epilepsy Congress, Kuala Lumpur, Malaysia in 2006.

Major goals of the diagnostic scheme for seizures and epilepsy proposed by the International League Against Epilepsy (ILAE) in 2001 (the 2001 Scheme), were to provide a standardized description of individual patients and to facilitate a logical clinical approach by applying the five axes, namely, ictal phenomenology (Axis 1), seizure types (Axis 2), epilepsy syndromes (Axis 3), etiology (Axis 4), and impairment (Axis 5), each of which has a recommended list (Engel 2001). The 2001 Scheme has been the subject of criticism in the clinical field, and continues to be amended so that it can become more matured and more useful diagnostic tool. However, the disagreements arose mainly from members of the Task Force on the Classification and Terminology of the ILAE Executive Committee (Wolf 2003, Engel 2003, Lüders *et al.* 2003, Berg and Blackstone 2003, Avanzini 2003, Engel 2006). Only a few studies have reported actual experiences of applying the scheme in the clinical field (Iinuma *et al.* 2006, Seino 2006, Mastrangelo *et al.* 2005, Akiyama *et al.* 2006). Furthermore, there are still fewer studies involving adult patients (Iinuma *et al.* 2006, Seino 2006).

Another important goal of the 2001 scheme was to facilitate incorporation of new epilepsy syndromes and to encourage further research, particularly in the field of genetic syndromes. More recently, the ILAE classification core group reported the revision of the notion of seizure types and epileptic syndromes, placing emphases on propagation patterns and age-at-onset, respectively (the 2006 Report) (Engel 2006). Although each of these items corresponds to Axis 2 and 3 in the 2001 Scheme, the 2006 Report does not include other axes or attempt to preserve the five-axis structure.

The aim of this study was to clarify the feasibility and clinical validity of the 2001 Scheme and the 2006 Report in adult patients with epilepsy. The abstract of this study was presented in workshops at the 39th and 41st Annual Meeting of the Japanese Epilepsy Society, Asahikawa in 2005, and Fukuoka in 2007, Japan, respectively, and in the 6th Asian and Oceanian Epilepsy Congress, Kuala Lumpur, Malaysia in 2006 (Kinoshita *et al.* 2007).

Patients and methods

We enrolled 100, consecutive, adult patients who visited the Neurology Clinic in Kyoto University Hospital at the beginning of January 2005 from the approximately 400 patients who regularly visited the Clinic specializing in epilepsy (Group 1). Data from at least one routine EEG (at least 30 min of awake and sleep recordings with electrodes set by the International 10-20 System) were available for all patients. Brain imaging was also performed for all patients using magnetic resonance imaging (MRI), or computed tomography (CT) when MRI was contraindicated. A single epileptologist (A.I.) was in charge of all patients in the clinic and applied the 2001 Scheme (Axes 1

to 4) and the 2006 Report (seizure types and epileptic syndromes) to each patient. The results were evaluated by another author (M.K.) for validation. We intended to exclude patients with pseudoseizures, but none presented during the period of enrollment in this group.

To evaluate the diversity of seizure semiology, we also enrolled 100, consecutive, adult patients with intractable epilepsy, who underwent prolonged scalp video-EEG monitoring in the Neurology Ward, Kyoto University Hospital for the purpose of diagnosis or presurgical evaluation for epilepsy surgery between January 1995 and August 2005 (Group 2). Four patients with pseudoseizures, one patient who had convulsive seizures caused by Hashimoto's encephalopathy, one five-year-old male patient, and nine patients with no reliable witness of their seizures, were excluded. Axis 1 of the 2001 Scheme was applied to each patient based on the diagnosis and seizure semiology recorded in the medical records, particularly in the video-EEG monitoring reports. One of the authors (M.K.) assembled the data and categorized all of the patients in this group.

Results

Below is an example description of one of the patients: S.M. a 26 year-old man, right-handed.

- No febrile convulsion, normal developmental milestones.
- Since the age 23, olfactory auras, auditory auras, *jamais vu* and mild disorientation occurred, each lasting less than 30 sec, independently, every 1-3 weeks, especially when tired or having a short sleep.
- One episode of sudden loss of awareness of 1 min at age 26.
- No abnormal neurological findings.
- WAIS-R: VIQ 120, PIQ 115, TIQ 118.
- EEG: frequent, irregular slow (3-5 Hz), regional left frontotemporal.
- MRI: mild left hippocampal atrophy.
- FDG-PET: regional glucose hypometabolism in the left temporal.
- Seizure (1981): simple partial seizure, complex partial seizure.
- Epilepsy (1989): symptomatic temporal lobe epilepsy.

The 2001 Scheme applied to this patient

- Axis 1: olfactory aura, auditory aura and mnemonic aura (*jamais vu*) – difficult-to-describe episodes of loss of awareness; the nearest category may be dyscognitive.
- Axis 2: focal sensory seizures with experiential sensory symptoms – impossible-to-express complex partial seizures with simple loss of awareness.
- Axis 3: Limbic epilepsy, mesial temporal lobe epilepsy with hippocampal sclerosis.
- Axis 4: possible hippocampal sclerosis.

The 2006 Report applied to this patient

- Seizure type: self-limited, focal, with contralateral spread to limbic areas.
- Epileptic syndrome: less specific age relationship, MTLT with HS.

In Group 1 (age 35.2 ± 12.2 years, mean \pm S.D.), 82% of the patients had fewer than one seizure a month, and 64% of patients had localization-related epilepsy (*table 1*). In Group 2 (age 29.0 ± 12.7 years, mean \pm S.D.), 84% of the patients had seizures more than once per week. In this group, 89% of the patients had localization-related epilepsy and there were none with idiopathic generalized epilepsy, because these patients were presumably candidates for focus resection (*table 1*).

There was some difficulty in categorizing symptoms into items in the glossary (II. Terms describing epileptic seizure semiology), Axis 1 in the 2001 Scheme (Engel 2001). Autonomic events fit into four categories (2.2.1.8, 3.0, 3.1, and 3.2): since Autonomic (2.2.1.8) and Autonomic aura (3.1) were essentially the same, only the former was used. As shown in the example above, it was difficult to describe episodes of loss of awareness, so Dyscognitive (2.3) was applied in these cases. It was also difficult and complicated to describe the body parts involved in each seizure (4.0-4.3.3). Incidence (5.1), Duration (6.0), and Severity (7.0) were essential factors for each patient and for each seizure, but they could not be expressed without concrete subcategories. Of the headlines, Somatotopic modifiers (4.0), Modifiers and descriptors of seizure timing (5.0), Duration (6.0), and Severity (7.0) could not be used as stand-alone items to indicate particular symptoms, whereas Motor (1.0), Non-motor (2.0), Autonomic events (3.0), Prodrome (8.0), and Postictal phenomenon (9.0) could be applied for symptoms in each category which could not be further specified.

Therefore, in this analysis, Autonomic aura (3.1), Somatotopic modifiers (4.0), Laterality (4.1), Unilateral (4.1.1), Hemi- (4.1.1.1), Generalized (4.1.2), Asymmetrical (4.1.2.1), Symmetrical (4.1.2.2), Body part (4.2), Centricity

(4.3), Axial (4.3.1), Proximal limb (4.3.2), Distal limb (4.3.3), Modifiers and descriptors of seizure timing (5.0), Incidence (5.1), Duration (6.0), and Severity (7.0) were excluded.

By applying the rest to Group 1, 184 items (8 Motor, 11 Non-motor, 2 Modifiers and descriptors of seizure timing, and 1 Postictal phenomenon) were listed and seizure semiology was precisely described, independent of the EEG (*table 2*). In Group 2, 333 items (10 Elementary motor, 9 Automatism, 17 Non-motor, 2 Modifiers and descriptors of seizure timing, 1 Prodrome, and 3 Postictal phenomenon) were listed (*table 2*). In particular, items not listed in Group 1 but listed in Group 2 mainly belonged to the Elementary motor (1.1) and Automatism (1.2) classification.

In Group 1, 145 seizures (generalized tonic-clonic seizures [GTCS]: 23%, complex partial seizures [CPS]: 29%, simple partial seizures: 21% and secondarily GTCS [2nd GTCS]: 21%), were defined according to the ILAE seizure classification (ILAE 1981). When Axis 2 (seizure types) was applied to Group 1, 126 seizures were labeled (GTCS, 26%; 2nd GTCS, 25%; focal motor seizures [FMS], 36%; and focal sensory seizures [FSS], 13%) (*figure 1*). Sixty-two percent and 26% of CPS, as defined by the 1981 seizure classification (ILAE 1981), were further categorized as FMS and FSS, respectively. However, the remainder of the seizures with loss of awareness only (24% of CPS, 10 seizures), fell into no suitable category. It was difficult to define spread patterns in the seizure types from the 2006 Report without a precise list of ictal phenomena. The majority of FMS with typical automatisms were labeled as focal onset with contralateral spread to limbic areas (dyscognitive) in accordance with the 2001 Scheme. However, in other focal seizures, impaired consciousness could not be identified. Thirteen seizures manifesting symptoms associated with limbic areas (asterisks in *figure 1*) were newly labeled.

By applying Axis 3 (epilepsy syndromes) to Group 1, 94 patients (94%) were categorized (*figure 2*). One patient with familial temporal lobe epilepsy, who could not be specifically designated, was able to be assigned to a specific category. Twenty-four patients with neocortical epilepsy, who could be further classified according to the 1989 classification, were grouped into the category of Symptomatic focal epilepsies - Neocortical epilepsies. Other types were defined by location and etiology. Five patients with Symptomatic generalized epilepsy, in Non-specific etiology, according to the 1989 classification, could not be labeled. Epileptic syndromes in the 2006 Report were assignable to 70% of patients. Twenty-five patients with idiopathic generalized epilepsy could not be categorized. All patients with neocortical epilepsy and limbic epilepsy, without hippocampal sclerosis, 50 patients in total, fell into the single category of Symptomatic focal epilepsies not otherwise specified.

Table 1. Epilepsy classification (1989).

	Group 1*	Group 2*
Localization-related epilepsies		
Temporal lobe epilepsy	35	54
Frontal lobe epilepsy	17	22
Occipital lobe epilepsy	2	4
Parietal lobe epilepsy	2	2
Partial epilepsy	8	7
Generalized epilepsies		
Idiopathic generalized epilepsy	27	0
Symptomatic generalized epilepsy	8	11
Undetermined	1	0

* Number of patients.

Table 2. Axis 1 (ictal phenomenology).

		Group 1 ^a	Group 2 ^a
1.1	elementary motor	3	1
1.1.1	tonic	1	19
1.1.1.2	postural	5	7
1.1.1.2.1	versive	2	23
1.1.1.2.2	dystonic	0	17
1.1.2	myoclonic	6	4
1.1.2.2	clonic	9	13
1.1.2.2.1	Jacksonian march	0	1
1.1.3.1	GTCS	63	31
1.1.4	atonic	0	3
1.2	automatism	21	7
1.2.1	oroalimentary	0	29
1.2.3	manual or pedal	0	31
1.2.4	gestural	0	4
1.2.5	hyperkinetic	0	14
1.2.6	hypokinetic	0	24
1.2.7	dysphasic	0	1
1.2.11	vocal	0	10
1.2.12	verbal	0	1
2.1	aura	0	9
2.2	sensory	0	1
2.2.1	elementary sensory	0	1
2.2.1.1	somatosensory	3	6
2.2.1.2	visual	4	3
2.2.1.3	auditory	4	1
2.2.1.4	olfactory	3	1
2.2.1.5	gustatory	0	21
2.2.1.6	epigastric	5	5
2.2.1.7	cephalic	2	1
2.2.1.8	autonomic	1	3
2.2.2	experiential sensory	1	6
2.2.2.1	affective	1	4
2.2.2.2	mnemonic	7	1
2.2.2.3	hallucinatory	0	1
2.2.2.4	illusory	0	2
2.3	dyscognitive	36	4
3.0	autonomic events	0	2
5.1.2	cluster	0	1
5.1.3.2	reflex	3	0
5.2	state dependent	3	2
8.0	prodrome	0	5
9.1	lateralising (Todd's)	0	1
9.2.1	impaired cognition	0	10
9.2.4	psychosis	1	2
Total		184	333

^a Number of items.

In 22 patients (22%) from Group 1, specific etiologies such as neurocutaneous disorders, malformations of cortical development, and tumors, were described in detail by applying Axis 4 (etiology) (*table 3*), adding important information for each patient which could not be expressed by Axis 2 or 3. However, hippocampal abnormalities, hereditary partial epilepsy, benign adult familial myoclonic epilepsy, and systemic lupus erythematosus were not listed in the classification of diseases frequently associated with epileptic seizures, in the 2001 Scheme. Four patients with so-called cryptogenic epilepsy remained unclassified.

Discussion

This study simply demonstrated the results of the practical application of the 2001 Scheme when employed in clinical situations as a diagnostic tool in adult patients.

Axis 1 was useful for precisely documenting patients' ictal semiologies, without considering the EEG information. Standardized technical terms are important to describe ictal symptoms, especially for non-specialists of epilepsy because, before defining epilepsy and epileptic seizures, they need to identify and diagnose epileptic features, or if unsure, consult epileptologists in emergency rooms or clinics. The cost of epilepsy misdiagnosis is currently high (Juarez-Garcia *et al.* 2006). Erroneous interpretation (over-read) of EEGs in non-epileptic seizures are important contributors to misdiagnosis (Benbadis 2006), thus appropriate semiological terms combined with proper knowledge of the symptomatology associated with the epileptic seizures, will help reduce misdiagnosis. Moreover, EEG is not always immediately available upon request even in urban areas, especially outside normal working hours (Quigg *et al.* 2001). In some rural areas in developing countries, where the diagnosis of epilepsy depends almost entirely upon clinical information because of financial and technological restrictions (Nicoletti *et al.* 1999, Onal *et al.* 2002, Tran *et al.* 2006), standardized description of seizure semiology, representing the neurophysiological features, is very helpful. Candidates for epilepsy surgery need precise evaluation of the diversity or stereotypy of the *semiology to delineate epileptogenic and symptomatic zones* (Luders *et al.* 1999, So 2006).

We encountered several difficulties in applying Axis 1 and 2 clinically. There was no term in the glossary to express episodes of loss of awareness with no other symptoms; in this study, we used the term "Dyscognitive (2.3)", because "dyscognitive seizures" is used in the 2006 Report to show involvement of mesial temporal limbic areas (Engel 2006). Similarly, Axis 2 lacks a category to show seizures with impairment of consciousness only. Axis 2 and seizure types in the 2006 Report rarely express consciousness disturbances in focal seizures, although wider spread is more often suspected in these seizures than in seizures

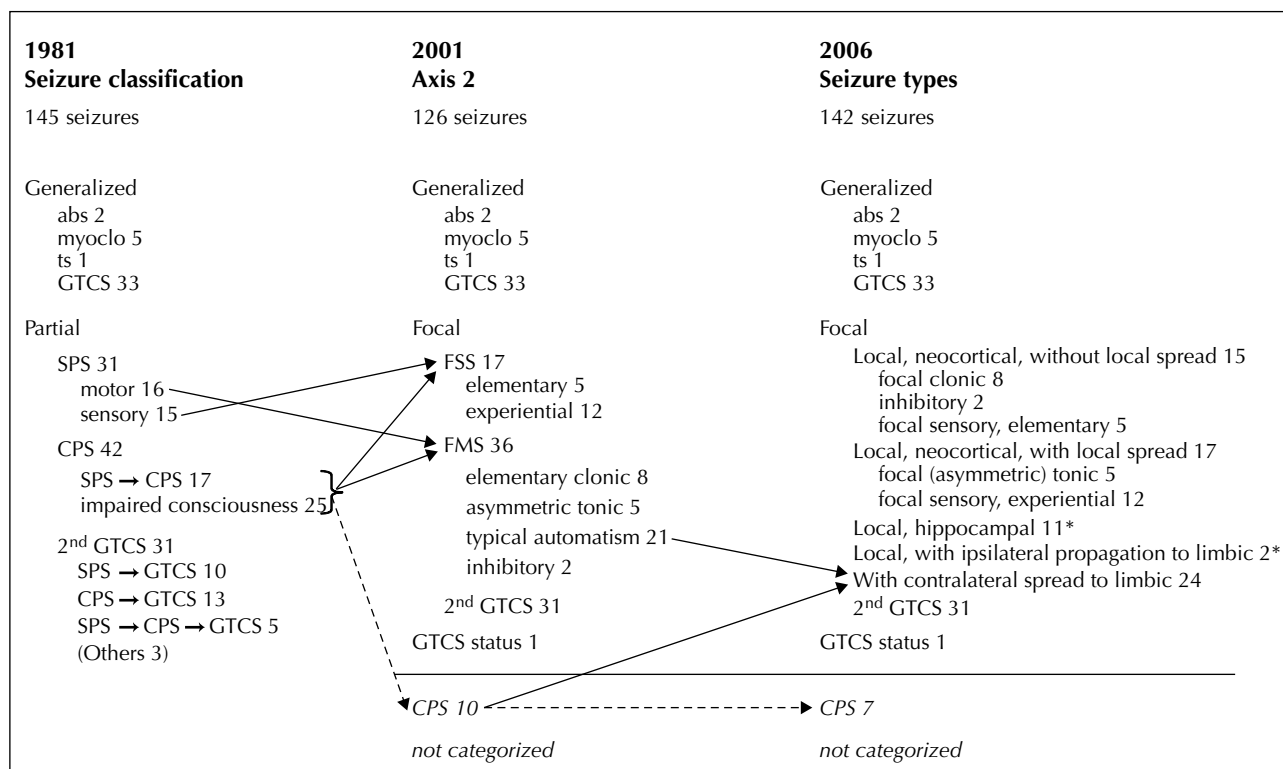


Figure 1. Seizure classification (1981), Axis 2 (Seizure type) in the 2001 Scheme and seizure types in the 2006 Report in Group 1. Of the complex partial seizures (CPS), as classified by the 1981 seizure classification and which exhibit impaired consciousness only, 23% cannot be categorized into Axis 2. GTCS: generalized tonic-clonic seizures; myoclo: myoclonic seizures; abs: absence seizures; TS: tonic seizures; SPS: simple partial seizures; FMS: focal motor seizures; FSS: focal sensory seizures; 2nd GTCS: secondarily generalized tonic-clonic seizures.

with preserved consciousness. From the results of the present study, the list of seizure types at least, needs to be revised. Considering the difference in the definitions and applications of the terms cognition and consciousness, the validity of applying the term dyscognitive to impaired consciousness needs to be discussed in order to reach a common consensus. Moreover, further studies are required to understand the mechanisms of epileptic loss of consciousness (Blumenfeld and Taylor 2003, Laufs *et al.* 2006). However, both the 2001 Scheme and the 2006 Report may be more applicable for a patient population of young children whose consciousness is often not well-defined during seizures.

In this study, we could categorize 94% of adult patients by applying Axis 3 (epilepsy syndromes), and 70% of them by the epilepsy syndromes of the 2006 Report. This ratio is higher than previous reports dealing with newborns (Mas-trangelo *et al.* 2005) or children (Akiyama *et al.* 2006), probably because of the difference in age group and institutional selection bias. We could not express epileptogenic zones of neocortical epilepsies from the 2001 Scheme, however, about one third of limbic epilepsies were included to comprise a large category of symptomatic focal epilepsies not otherwise specified in the 2006

Report. In the 2001 Scheme, we were unable to label patients with non-specific symptomatic generalized epilepsy according to the 1989 classification, and the majority of idiopathic generalized epilepsy would not fit into a suitable category in the 2006 Report. It would be worthwhile to discuss whether corresponding, additional categories are needed.

Application of Axis 4 helped in understanding the patients' current and possibly future states. We were able to identify several diseases and conditions frequently associated with epileptic seizures, which were not listed in the 2001 Scheme.

The whole composition of the diagnostic scheme could be clarified, especially as regards how to deal with the five-axis structure of the 2001 Scheme. To determine the spread patterns of seizure types in the 2006 Report, we would like to have a revision of the list for Axis 1 with a more precise correspondence to them. Hippocampal sclerosis is specified in the lists for Axis 3 and epilepsy syndrome in the 2006 Report and thus needs to appear in the list for Axis 4.

The major limitation of the current study is that it serves as a feedback from the clinical field in adult patients, and therefore, it is still unknown whether further studies of other

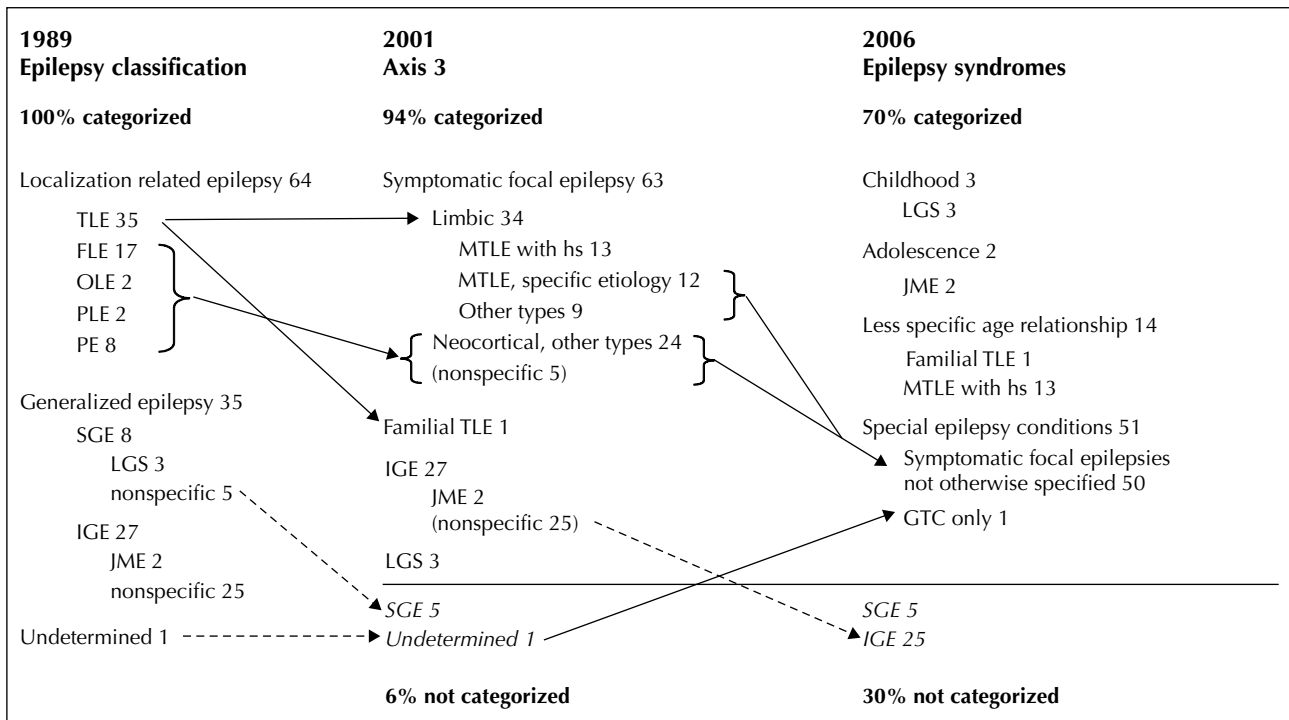


Figure 2. Epilepsy Classification (1989), Axis 3 (epilepsy syndromes) in the 2001 Scheme and epilepsy syndromes in the 2006 Report in Group 1. 100%, 94% and 70% of patients are sorted, respectively. Symptomatic generalized epilepsy (SGE) and idiopathic generalized epilepsy (IGE) with non-specific etiology lack suitable categories. Neocortical epilepsy and non-specific limbic epilepsy are grouped together to comprise symptomatic focal epilepsies not otherwise specified. TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy; OLE: occipital lobe epilepsy; PLE: parietal lobe epilepsy; PE: partial epilepsy; JME: juvenile myoclonic epilepsy; LGS: Lennox-Gastaut syndrome; MTLE: mesial temporal lobe epilepsy; hs: hippocampal sclerosis.

Table 3. Axis 4 (Etiology): Group 1.

Etiology	Number of patients / 100
Neurocutaneous disorders:	
tuberous sclerosis complex	1
Malformations of cortical development:	
focal cortical dysplasia	6
Hemimicroencephaly*	1
Tumors:	
cavernous angioma	2
other	10
Postnatal infections:	
other	1
Other postnatal factors:	
head injury	1
stroke	1
Hippocampus abnormalities*	14
Hereditary partial epilepsy*	6
Benign adult familial myoclonic epilepsy*	1
Systemic lupus erythematosus*	2

* These terms are not listed in the classification of diseases frequently associated with epileptic seizures in the 2001 Scheme.

patient populations, such as children or those with very severe epileptic encephalopathy, will reveal similar results. In addition, the analyses here were performed essentially by one doctor for each group and inter-rater disagreement was not evaluated. However, we consider it as valid because previous studies have shown high inter-rater reliability (Kellinghaus *et al.* 2004, Baykan *et al.* 2005).

Further feedback from clinical fields in different kinds of patient populations is very important to establish a more widely acceptable and practical diagnostic scheme, to achieve a common consensus for clinical application, and to elaborate notions of new diseases or entities, which would lead to novel therapeutic approaches. □

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