Epileptic Disord 2006; 8 (1): 81-5

Are epilepsy classifications based on epileptic syndromes and seizure types outdated?

H.O. Lüders[1], J. Acharya[2], A. Alexopoulos[1], C. Baumgartner[3], J. Bautista[1], R. Burgess[1], M. Carreño[4], B. Diehl[1], D. Dinner[1], A. Ebner[5], N. Foldvary[1], J. Godoy[6], H. Hamer[7], A. Ikeda[8], K. Källén[9], C. Kellinghaus[10], P. Kotagal[1], D. Lachhwani[1], T. Loddenkemper[1], J. Mani[11], R. Matsumoto[8], G. Möddel[10], D. Nair[1], S. Noachtar[12], C.A. O'Donovan[13], S. Rona[14], F. Rosenow[15], S. Schuele[1], C.A. Szabo[16], N. Tandon[17], A. Tanner[1], P. Widdess-Walsh[1]

[1] Epilepsy Center, Cleveland Clinic Foundation, Cleveland, OH, USA
[2] Epilepsy Center, St. Louis University, St. Louis, MO, USA
[3] Department of Neurology, Medical University of Vienna, Vienna, Austria
[4] EEG and Epilepsy, Hospital Clinic, Barcelona, Barcelona, Spain
[5] Epilepsy Surgery Program, Bethel, Klinik Mara, Epilepsy Center, Bethel, Bielefeld, Germany
[6] Departmento de Neurolgia, Universidad Católica De Chile, Santiago, Chile
[7] Epilepsy Center, University of Marbug, Marburg, Germany
[8] Comprehensive Adult Epilepsy Center, Kyoto University Hospital, Kyoto University, Kyoto, Japan
[9] Section of Epilepsy, Lund University Hospital, Lund, Sweden
[10] Epilepsy Centre, University of Münster, Münster, Germany
[11] Neurologist, Mumbai, India
[12] Epilepsy Center Munich, University of Munich, Munich, Germany
[13] Comprehensive Epilepsy Center, Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA
[14] Epilepsy Center, University of Freiburg, Freiburg, Germany
[15] Interdisciplinary Epilepsy Center, University Hospitals, Philipps University, Marburg, Germany
[16] South Texas Comprehensive Epilepsy Center, University Texas Health Science Center at San Antonio, San Antonio, TX, USA
[17] Epilepsy Surgery, Dept of Neurosurgery, University of Texas Health Science Center - Houston, Houston, TX, USA

Received January 13, 2006; Accepted February 1, 2006

Correspondence:
H.O. Lüders
Epilepsy Center,
Cleveland Clinic Foundation,
Cleveland, Ohio,
USA

We appreciate the careful and thoughtful review by Dr Engel of the manuscript we published on the Cleveland Clinic Epilepsy Classification (CCEC) (Loddenkemper *et al.* 2005, Engel 2005).

Dr Engel is correct when he concludes that one of the main differences between the CCEC and the ILAE Epilepsy Classification (ILAE-EC) is the reliance of the ILAE-EC on epileptic syndromes and epileptic seizures as essential building blocks of the classification.

Usefulness of epileptic syndromes will become obsolete in the near future

Let us analyze first the reason we feel that syndromatic epilepsy classifications has become or will become obsolete in the near future. Diagnostic tools developed over the last 20-30 years have dramatically increased our ability to pin point the etiological processes that lead to epileptic seizures. We know now that essentially all

• Epileptic seizures are always due to multiple etiologies (poly-etiological)
• Seldom a predominant etiology produces a relatively uniform phenotype
• We will be able to identify most of the etiological factors in the near future
• Prognosis and management will then depend on better understanding of how these etiological factors influence the epilepsy

epilepsies are the consequence of numerous etiologies each influencing in varying degrees the clinical expression of the epilepsy (for example, seizure semiology and seizure frequency). It is true that in certain cases one etiological factor may predominate (for example patients with cavernous angiomas in the temporal neocortex). But even in these cases other factors, such as susceptibility and modifier genes, may influence the clinical expression of the epilepsy with some patients not having any seizures, others having infrequent focal seizures and finally a group of patients that may have pharmacologically intractable secondarily generalized motor seizures. The situation is becoming even more complicated for those cases in which there is primarily a genetic defect as the main etiology of the epilepsy. There is now abundant evidence that epileptic patients from families suffering from epilepsy produced primarily by a single gene very frequently have different semiological seizure types and if classified syndromatically would have different epilepsy syndromes. This again, is most probably produced by the polygenic nature of the disease, namely different modifier and susceptibility genes would lead to different seizure phenotypes. From these considerations we can conclude that the search for a "biological taxonomy" or "diagnostic entities equivalent to natural classes" will become more and more elusive as our ability to identify the different etiologies that produce or modify the expression of epilepsy become easier to identify. The available evidence suggest that we do not have a finite number of epilepsy syndromes but individual epileptic patients each with specific epileptic seizures arising from a defined location of the human cortex and determined by numerous etiologies including numerous modifier and susceptibility genes. Here is the fundamental difference between the ILAE-EC and the CCEC. The ILAE-EC tries to fit each patient into a syndromatic epilepsy group assuming that these are "diagnostic entities equivalent to natural classes". The definition of an epileptic syndrome itself required consensus between the ILAE Work Force on at least seven categories such as age of onset, EEG, and interictal symptoms and signs. The CCEC, on the other hand, recognizes that epilepsy patients are best categorized by defining the site of origin of the seizures, the semiological characteristics of the seizures, its frequency and most importantly the essential etiological factors (including all the susceptibility and modifier genes as well as genes that may predict the response to antiepileptic drugs). Therefore, the main emphasis of the CCEC is the objective classification of these factors: epileptogenic zone, seizure semiology, seizure frequency, and most importantly etiologies. Together with the related medical conditions and in the future, genetic factors that permit predicting response and reaction to anticonvulsants, we have all the information necessary to manage the patient and to define prognosis. Besides, definition of all these factors also permits syndromatic classification if the patient happens to fall into one or another syndromatic category. In those cases, the definition of a syndrome, as Dr Engel mentioned, may be useful because a single expression (the epileptic syndrome) may identify some of the features classified in more detail within the CCEC and not a separate categorical system.

Epileptic syndromes have never been defined scientifically

• Epileptic syndromes are constellations of symptoms and signs that tend to occur together
• Syndromes have not been defined by scientific methodology
• "Lumpers" will define broad categories with more limited prognostic and management value. "Splitters" will define more specific groups with more prognostic or management value

It is important to consider at this point what an epileptic syndrome actually consists of. An epileptic syndrome is nothing more than a combination of semiological seizure types arising from a more or less well defined epileptogenic zone, associated with a certain number of neurological symptoms, and produced by a finite number of etiologies. Broad definition of each one of those categories results in a more restricted number of syndromes. On the other hand, a more strict definition of each one of these factors leads to a larger number of identifiable syndromes. The extreme is the CCEC, in which essentially each of these factors is classified individually leading to an almost infinite number of "syndromes". Obviously, the more precisely we define a syndrome the higher its value in defining prognosis and its response to antiepileptic medication. Are there any rules that we can use to determine the best way to lump different constellations into a specific number of syndromes? To quote Ann Berg (Berg and Blackstone 2003): "Implicitly one must be prepared to split before one can lump. Thus we can always be on guard against unwittingly lumping because we are unaware of certain characteristics on which we should have split". There is no doubt that we could use mathematical approaches (i.e. cluster

analysis, etc) to define the "ideal" syndromes, namely those constellations that provide the highest predictive power regarding prognosis and response to therapy. Unfortunately, such an approach is difficult and, interestingly, would require the definition of an objective classification of the different factors that define the syndromes, i.e. a classification similar to the CCEC. There never has been an attempt to define objectively epileptic syndromes by a scientific approach, possibly also because of the lack of adequate classification tools until today.

Arbitrary definition of "accepted" epileptic syndromes would have a major impact on the everyday practice of clinical epilepsy and on future clinical research in epilepsy

- The ILAE Task Force's definition of epileptic syndromes and seizures is based upon consensus and not upon scientific methodology
- Acceptance of the ILAE-EC would establish these "constellations of symptoms and signs" (epileptic syndromes) as the basis for future patient management and clinical research
- This could limit future advances, particularly if less restrictive alternative approaches to classification exist

The ILAE-EC decided on "accepted" epileptic syndromes by polling the members of the Task Force. Considering the extensive experience and wisdom of the members we can expect that the selected epileptic syndromes are most likely those that in the past have been most useful in everyday practice. However, as we mentioned above, we are facing a rapid evolution of our diagnostic tools. In the coming decades we will dramatically increase our diagnostic armamentarium. Identification for each patient with epilepsy of specific genes that cause epilepsy as well as general susceptibility genes and modifier genes will be possible. In addition, for each patient we will be able to perform genetic testing that defines the response to medications and adverse effects to medications. We need a classification system that does not bind us to a relatively arbitrary lumping of signs and symptoms but takes into account the new face of epilepsy diagnosis and allows us to analyze objectively the influence of different etiological factors on the different building blocks of epilepsy (epileptogenic zone, semiology, seizure frequency, related medical conditions and perhaps others). We have to realize that epilepsy as a poly-etiological disease has no "natural classes". The task of the future is a better understanding of the effect of different etiological factors on the phenotypic expression of epilepsy in any given individual. As a poly-etiological entity we will also have to understand the interaction of the different etiologies. To achieve this, we need an objective phenotypic epilepsy classification without any preconceived notions. The CCEC is one example of an epilepsy classification in which most of the phenotypic epilepsy manifestations have been classified by objective criteria.

The ILAE-EC specifies epileptic seizures as "unique diagnostic entities" without given objective criteria of the methodology used to define them

- In the ILAE-EC epileptic seizures are "unique diagnostic entities" because of a unique pathophysiology, unique neuronal substrate, unique response to AEDs, unique EEG pattern, ictal propagation or occurrence in specific epileptic syndrome
- The ILAE Task Force members decided by "vote" which seizures would actually constitute a "unique diagnostic entity"
- The same as for epileptic syndromes, this methodology creates categories that may be artificial and may limit future research
- Objective classification of epileptic seizures by semiology (CCEC) leaves the door open for scientific correlation studies between etiologies and phenotypic seizure expression

Another major difference between the ILAE-EC and the CCEC is the approach to classification of epileptic seizures. The ILAE-EC classifies epileptic seizures as "unique diagnostic entities" defined by a number of criteria, namely pathophysiological mechanisms, neuronal substrate, response to AEDs, EEG ictal patterns, propagation and postictal features, and association with special epileptic syndromes. Again no objective criteria are used to define what a unique diagnostic entity is and it was assumed that the members of the ILAE EC task force, all of whom are experienced epileptologists, would make a wise decision selecting what is or not an epileptic seizure. This approach, however, by setting specific boundaries may limit our ability to unravel specific etiologic factors that may be related to yet undescribed "epileptic seizure types". Besides, similar to epileptic syndromes, epileptic seizures may be the foundation for future research. The results of this research can only be as good as the building blocks are. Therefore, a priori definition of epileptic seizures as unique diagnostic entities, may lead to misleading results if for any reason the initial definition of the epileptic seizures was inaccurate or too restrictive. On the other hand, epileptic seizures classified by a single objective criterion like semiology, leaves the door open for

unbiased, scientific correlation studies between etiologies and phenotypic seizure expression.

The commentary includes several misinterpretations which we would like to correct

- It is correct that the CCEC includes a detailed semiological seizure classification. It is not true, however, that the CCEC emphasizes semiology over other facets of epilepsy classification
- It is not true that the semiological classification or any other dimension can not be used for clinical or basic research purposes
- We have provided clear proof, including the objective analysis of an linguistic expert, that the Cleveland Clinic Semiological Seizure Classification is a classification and not just a "description of ictal phenomenology" (Wiese 2004)
- It is not true that axis 1 of the ILAE-EC, a seizure glossary, is the same as the semiological seizure classification
- In many patients it is not true that localization of the epileptogenic zone is "extremely" difficult
- It is not true that it is an "omission" that there is no independent axis in the CCEC classifying epileptic seizures as special diagnostic entities
- It is not true that classification of the epileptogenic zone provides little or no information

Dr Engel's remarks that the "basic premise of the Cleveland Clinic diagnostic approach has been that emphasis should be placed on a detailed description of the ictal events" is misleading. We certainly stress accurate assessment of all 5 dimensions included in the CCEC and do not feel that necessarily one axis is more important than another. The emphasis is in the accurate and *objective* description of the 5 dimensions, each one of them classifying *objectively and independently* different facets of the epilepsy.

We certainly disagree that the CCEC can not be easily organized into categories to constitute a useful classification for clinical or basic research purposes. We have used this classification in most of the research efforts and publications from this group demonstrating that the classification can be used effectively in research projects (Acharya *et al.* 1997, Hamer *et al.* 1999, Henkel *et al.* 2002, Kallen *et al.* 2002, Kellinghaus *et al.* 2004, Loddenkemper *et al.* 2004, Noachatr *et al.* 1999, Schlaug *et al.* 1997, Usui *et al.* 2005, Wehrhahn *et al.* 2000).

Many investigators have argued before that the CCEC, probably because of its simplicity, is not a classification but just a description. That is not true. We had a linguistic expert who analyzed the information and concluded that in English as also in other languages (including German) the CCEC was a classification (Wiese 2004). Unfortunately this article was published in German but includes an abstract in English

Axis 1 of the ILAE-EC is a glossary. The intention of the Task Force working in its design received the clear mission not to make a classification (i.e. grouping seizures by semiology) but to only define terms used to describe seizure semiology. A glossary does not communicate the components of a single seizure, the level of consciousness, or lateralizing features as the CCEC semiological classification does. Furthermore, without an orderly approach to describing seizure semiology, "allowing the physician to determine the degree of descriptive detail" would create a heterogeneous mix of terms that is practically useless. The Cleveland Clinic seizure classification was designed specifically to classify seizures based exclusively on precisely defined ictal semiological categories.

It is not true that determination of the epileptogenic zone is extremely "difficult". In most cases, just by taking the clinical history we can make a good assessment of the likely epileptogenic zone. As we obtain additional clinical information (i.e. EEG, neuroimaging, etc) we usually confirm our initial impression, increase the confidence with which we have defined the epileptogenic zone and define it with added precision.

The CCEC classifies seizures by semiology in dimension 2. This permits classification of the seizures by an objective criterion which is completely independent of all other parameters classified in the other 4 dimensions. We feel, as outlined above, that trying to identify seizure types based on multiple criteria some interdependent on the other dimensions of classification (for example, occurrence of the seizure type in specific epileptic syndromes) is confusing and could negatively impact research efforts. Therefore, the absence of epileptic seizure type as a diagnostic entity in the CCEC was done purposefully and certainly is not an omission.

We certainly disagree with Dr Engel's comment that "classification of the epileptogenic zone (EZ) provides little or no information". Sorting epilepsies into different categories such as generalized or focal has been part of previous ILAE proposals and may therefore well serve as a classification. Besides, the localization of the EZ usually provides information if epilepsy surgery is warranted, and in conjunction with information from other dimensions of the CCEC it assists us in deciding what kind of additional investigations are necessary. It has also not been infrequent to have patients referred to our Center with the label of "Lennox-Gastaut Syndrome" or "West Syndrome" who eventually became seizure-free after resection of a focal epileptogenic zone. This shows that an individual patient-oriented classification bears relevance in everyday practice.

Conclusion

- We appreciate the careful review by Dr Engel of the CCEC
- The ILAE-EC includes epileptic syndromes and seizure types as diagnostic entities in two of their dimensions
- The definition of epileptic syndromes and seizures follows no scientific method and is decided by "vote" of the ILAE Task Force
- The different axes of the ILAE-EC define interrelated parameters
- All these factors could limit significantly the usefulness of the ILAE-EC for management and research purposes

We certainly appreciate Dr Engel's review and his critique of the CCEC. Both the ILAE and the Cleveland Clinic group embarked on the task to design a new epilepsy classification because the 1981/1989 ILAE classification systems did not fulfill our needs, from a patient management point of view as well as for research purposes. Interestingly, the paths we followed were divergent.

The ILAE put the greatest emphasis on the definition of epileptic syndromes and epileptic seizure types as diagnostic entities. These entities were not defined by any scientific method but by vote of the members of the ILAE Task Force. They also worked completely in the theoretical sphere without any attempt (at least so far) to test the system they have developed in the practical field (either patient management or research). They made no attempt to define independent axes but developed a classification in which at least the first 3 axes have significant overlap. We feel that approval of the proposal of the ILAE-EC proposed by this Task Force, if indeed it is user friendly and is adopted extensively by researchers and epileptologists, could significantly slow the future development of epileptology. Classifications form the basis of research efforts and also of every day management decisions. However, since these building blocks (epileptic syndromes and epileptic seizure types) were defined by "impressions" of experts in the field there is significant room for error. The results from research efforts which use these predefined foundation stones in their research efforts can not reach correct conclusions if these foundation stones were not defined correctly.

The CCEC on the other hand was designed primarily to avoid any bias. Each axis is defined by objective criteria and special care was taken to avoid overlap of axes. Independence of the different axes allows for correlation research between its factors. Besides, by avoiding lumping of factors (epileptic seizure types, epileptic syndromes) we open the door for research that would eventually define in an objective fashion which factors have associations and the strength of these associations. Considering that the future diagnostic capabilities will undoubtedly uncover many etiologies for the epilepsies, such an unbiased approach to classification is essential. Besides, to make sure that the classification can be used in clinical practice we have tested the system over more than 15 years in different epilepsy centers throughout the world. This approach led to numerous revisions, the product of which was recently published in *Epileptic Disorders*. □

References

Acharya JN, Wyllie E, Luders HO, Kotagal P, Lancman M, Coelho M. Seizure symptomatology in infants with localization-related epilepsy. *Neurology* 1997; 48: 189-96.

Berg A, Blackstone NW. Of cabbages and kings: perspectives on classification from the field of systematics. *Epilepsia* 2003; 44: 8-12.

Engel Jr. J. Classification is not EZ (Invited Editorial Comment). *Epileptic Disord* 2005; 7: 317-20.

Hamer HM, Wyllie E, Luders HO, Kotagal P, Acharya J. Symptomatology of epileptic seizures in the first three years of life. *Epilepsia* 1999; 40: 837-44.

Henkel A, Noachtar S, Pfänder M, Lüders HO. The localizing value of the abdominal aura and its evolution: a study in focal epilepsies. *Neurology* 2002; 58: 271-6.

Kallen K, Wyllie E, Lüders HO, Lachhwani D, Kotagal P. Hypomotor seizures in infants and children. *Epilepsia* 2002; 43: 882-8.

Kellinghaus C, Loddenkemper T, Dinner DS, Lachhwani D, Lüders HO. Seizure semiology in the elderly: a video analysis. *Epilepsia* 2004; 45: 263-7.

Loddenkemper T, Wyllie E, Neme S, Kotagal P, Lüders HO. Lateralizing signs during seizures in infants. *J Neurol* 2004; 251: 1075-9.

Loddenkemper T, Kellinghaus C, Wyllie E, Najm IM, Gupta A, Rosenow F. LüdersHO. A proposal for a five-dimensional patient-oriented classification. *Epileptic Disord* 2005; 7: 306-16.

Noachtar S, Lüders HO. Focal akinetic seizures as documented by electroencephalography and video recordings. *Neurology* 1999; 53: 427-9.

Schlaug G, Antke C, Holthausen H, *et al.* Ictal motor signs and interictal regional cerebral hypometabolism. *Neurology* 1997; 49: 341-50.

Usui N, Kotagal P, Matsumoto R, Kellinghaus C, Luders HO. Focal semiologic and electroencephalographic features in patients with juvenile myoclonic epilepsy. *Epilepsia* 2005; 46: 1668-76.

Werhahn KJ, Noachtar S, Arnold S, *et al.* Tonic seizures: their significance for lateralization and frequency in different focal epileptic syndromes. *Epilepsia* 2000; 41: 1153-61.

Wiese R. Über das Klassifizieren - eine linguistische Anmerkung. *Z Epileptol* 2004; 17: 235-43.