Epileptic Disord 2006; 8 (2): 159-63

Debate on the classification of epileptic seizures and syndromes

Are epilepsy classifications based on epileptic syndromes and seizure types outdated?

Letter to the Editor

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Lüders and his colleagues (Lüders *et al*. 2006) are confusing classifications with diagnostic manuals. Although there may be value in discussing advantages and disadvantages of the Cleveland Clinic's five-dimensional diagnostic scheme (Loddenkemper *et al*. 2005) over the ILAE's five axes diagnostic scheme for individual patients, neither addresses the need for one or more new classification systems that will allow categorization of relatively homogeneous patient populations for a variety of purposes such as basic research into fundamental mechanisms, drug trials, and epidemiological studies. Dividing people with epilepsy into meaningful groupings that have etiologic, therapeutic, and prognostic implications, and can be easily applied worldwide, is also essential for teaching and easy communication among physicians. Diagnostic manuals do not serve this purpose, even if they provide excellent opportunities to precisely describe individual patients. Classifications based on syndromes and seizure types provide a simple and rapid way to uniformly identify similarities and differences among patients for clinical care, research, and teaching. In fact, the success of endeavors underway today to identify underlying genetic mechanisms for epilepsy would have been impossible without first having biologically relevant classes of epilepsy to serve as the phenotype.

Contrary to the assertions of Lüders *et al*. (2006), it is unlikely that we will be able to identify most of the etiologic factors of epilepsy in the near future, particularly because (as these authors note) epileptic seizures almost always result from a confluence of multiple causes. Also contrary to their assertion, accurate localization of the epileptogenic zone requires detailed expensive diagnostic evaluation, most of which is not justified unless surgical treatment is considered.

We agree that at the present time the designation of specific epilepsy syndromes and epileptic seizure types are based more on clinical experience and expert opinion than on scientific principles. Syndromes can be treated as hypotheses that are constantly remodelled on the basis of insights derived by studying patient groups. This syndrome concept has been valuable up to a point; however, at this juncture more is needed. The ILAE Commission on Classification is beginning to develop scientific and evidence-based approaches to defining and recognizing these diagnostic entities as distinct conditions. We also agree that classification systems can engender inappropriate rigid thinking; therefore, it is essential that syndrome or seizure type diagnoses not be used in a dismissive fashion to avoid considering each patient as an individual. Any classification must be constantly reevaluated, challenged, and revised as necessary, and clinical care must always be based on features of individual patients, whether or not a specific diagnosis can be made.

Finally, to set the record straight, the statement by Lüders *et al*. (2006) that "The ILAE-EC tries to fit each patient into a syndromatic epilepsy group assuming that these are diagnostic entities equivalent to natural classes" is simply wrong. Although studies can be cited that diagnosed a higher percentage of patients with specific syndromes than those studies cited by Lüders *et al*., the ILAE has acknowledged in every publication that not all patients can be assigned a syndromic diagnosis. However, when a syndromic diagnosis cannot be made, a diagnosis of one or more specific seizure types usually can. At this point, the ILAE does not assume that diagnostic entities are equivalent to natural classes, but the concept of natural classes

provides a useful framework for our ongoing evidence-based approach to classification. Their statement that "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" suggests that they misunderstand the scientific process. Classification is essential to hypothesis testing. All biological systems have natural classes, and further scientific inquiry will only improve our ability to identify natural classes of epilepsy disorders. This has certainly been the case for virtually all other neurological disorders and more generally throughout medicine and biology. Epilepsy presents unique and complex challenges but ultimately it too should be subject to the same scientific principles that guide investigation into the many other disorders that affect the brain.

Key words: epilepsy classification, seizure classification, epilepsy genetics, etiology of epilepsies, epilepsy classification task force

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The non-neurologists' view on epilepsy syndromes classification

Letter to the Editor

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Despite major advances in imaging and molecular techniques that aid in the diagnosis of epilepsy, the issues of classification are far from solved. Identification of mutations in genes causing epilepsy has increased our understanding of the underlying etiologies of epilepsy. However, we are not yet at the point where a neurologist can perform a blood test on a patient and determine all the genes that are causing their epilepsy or predict response to medication. So without all the answers, why try to discard one of the tools that has proved so helpful in the search to further understand epilepsy, the International League Against Epilepsy – Epilepsy Classification (ILAE-EC).

Lüders and colleagues (Lüders *et al*. 2006) claim that syndromology will become obsolete in the future because all epilepsies are likely to have numerous etiologies and that knowledge of these is necessary to predict appropriate management and treatment. It is true that many epilepsies are polygenic or complex in nature and that the phenotype of the patient may well be dependent on both genetic and environmental factors. Unfortunately we are still some way from understanding the extent of these factors and being able to apply this knowledge in clinical practice.

A primary concern seems to be publications reporting large percentages of patients that cannot be classified using the current ILAE-EC. As non-medical research assistants in an epilepsy research team, we are trained to "diagnose" a range of both the common and the complicated epilepsy patients using the current classification. This is achieved through a detailed questionnaire including patient and eye-witness accounts and critical analysis of patient medical records (Reutens *et al*. 1992). From our combined epilepsy research experience of fourteen years, it is rarer for us to find individuals that cannot be classified than to fail to make a syndrome diagnosis. From scrutinising medical records written by numerous neurologists, it seems that many do not use the current classification tools in the general clinical setting. Perhaps this is part of the problem and the issue is more one of teaching physicians how to use the classification as a practical clinical tool in approaching diagnosis and optimizing management.

Criticism has emerged regarding the methods by which the current ILAE classification was developed. The argument was that consensus of the Task Force to determine syndromology is an "unscientific" basis for classification. Often the most practical method for classifying epilepsies is through clinical observation and then applying those findings in a way that will benefit patients. In our own research, we have seen new syndromes evolve as hypotheses, that are then tested and confirmed by new families. In genetic research, a particular genetic defect may ultimately validate the novel syndrome (e.g. generalised epilepsy with febrile seizures plus).

The authors claim that epileptic syndromes are merely "constellations of signs and symptoms that tend to occur together" arising from one epileptogenic zone and that focusing on these groupings as syndromes is too restrictive. Yet splitting patients into groups using descriptions that are too precise is not useful in many clinical and research

settings. Moreover, it can represent "false precision" in terms of the variability that we see in all natural systems. Syndromes are developed by looking for patterns across patient populations and investigating which seizure types cluster, the ages of onset of seizures and how they associate with certain EEGs, MRIs, intellectual functioning, regression etc. Focussing on seizure descriptions does not provide information about how a patient's epilepsy may progress or which antiepileptic medications will be most effective in controlling their epilepsy.

Proof of the utility of epilepsy syndromes can be seen in a variety of areas. For example, success in identifying the gene causing most cases of Dravet syndrome would not have been possible without the initial recognition of the syndrome by Charlotte Dravet. Thus rather than becoming obsolete, syndromes remain the key to unlocking the secrets and biological complexity of epilepsy. In our view, the "art" of epilepsy syndromes is deciding where to draw the line between excessive splitting (false precision) and lumping of cases. Syndromes undergo continual modification to reflect new discoveries and rather than being monolithic entities decided solely by a committee. Again, Dravet's syndrome is an excellent example. Dr Dravet's brilliant insight into the gestalt of this syndrome of a previously extremely difficult to categorize epilepsy has led to better recognition and treatment of these children as well as the discovery of the underlying genetic defects. It has since been recognised that myoclonic seizures are not always present, or at least prominent, in Dravet's syndrome and the syndromic description has been appropriately modified. Such revolutionary improvement in diagnosis, treatment, classification and subsequent molecular discovery would have been impossible with the seizure orientated CCEC proposal.

One must bear in mind when attempting to classify patients with any complex disease that there are no *a priori* "natural" classes. Syndromes are man-made constructs developed to help consolidate large amounts of information into a form that can be used diagnostically and as a guide to management and prognosis. Therefore, there is no right and wrong, apart from establishing what is the most *useful* system for the job at hand. In the case of epilepsy, the classification system must prove useful in both clinical practice and research, and be amenable to change based on new observations. The proposed CCEC is currently very limited in that it is almost solely beneficial in the clinical setting and even then, predominantly for surgical candidates with focal epilepsies.

As a clinical researcher, the primary focus is the patient. The CCEC claims to be patient-oriented and although the classification is very patient specific, in non-surgical cases it will not be useful for the patient or the clinician in determining the probable course or the best treatment for their epilepsy, nor for advancing the science of epileptology.

Keywords: epilepsy classification, seizure classification, epilepsy genetics, etiology of epilepsies

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Epilepsy syndromes still survive

Letter to the Editor

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As our knowledge increases, it is very appropriate for us to re-ask the same question: "Why bother with epilepsy syndromes?" Are the answers to this question the same as before? Are the answers still relevant?

Particularly in childhood and adolescence, the epilepsies or the epilepsy syndromes cover such a wide range, from the relatively benign to very handicapping, that it is essential to have a language that will easily allow us to distinguish between them. Identification of the syndrome provides an indication of the types of treatment that are likely to be of benefit and also provides information on the likely prognosis. Prognosis includes not only the outlook in terms of seizure control, but also in terms of cognition and behaviour, factors that affect the life of the child profoundly. Would the Cleveland classification (Loddenkemper *et al*. 2005, Lüders *et al*. 2006) fulfil these requirements? It certainly would not provide a simple way of communicating with parents, patients and colleagues in the way that epilepsy syndromes do. However, this type of multi-axial approach may be very useful in describing the clinical state of a patient at a point in time and of tracking the patient's progress. It also provides some sort of framework when a syndrome diagnosis cannot be made. Does it provide much more than the proposed ILAE classification scheme? The latter depends primarily on the identification of epilepsy syndromes or, when this is not possible, on seizure

types. It also provides a multi-axial framework that covers similar areas to that of the Cleveland classification. When the 1981 ILAE classification was announced, it was clear that there was ongoing disagreement but this step nevertheless achieved something very important. Even if clinicians thought that the scheme had its shortcomings, the terminology was almost universally adopted, with the major implication that colleagues could communicate with each other in terms that were nationally and internationally used: the seizure type and subsequently the epilepsy syndrome that the patient had were relatively likely to be described in similar technical terms by different epileptologists, wherever they were. Both patient management and scientific research have benefited greatly.

Clinicians know very well that many patients have epilepsy that cannot be classified into an epilepsy syndrome but when it can, this classification can be very helpful in management. The situation is further complicated by the fact that we expect that most "idiopathic" epilepsies will have to be reclassified as "symptomatic" when genetic causes have been identified, that several different genes seem to underlie a single syndrome and that several different clinical epilepsy syndromes can occur in the same family. Perhaps in the future the possibility that any classification could omit the type of channelopathy will be met with derision. Against this changing scientific background, it is almost inevitable that terminology will be revised and will change. However, there are three important principles that must be maintained throughout. First, the terminology must be simple enough to allow clear communication. Second, it must be used universally adopted, to avoid adding confusion to an already complex field. Third, it must be clinically relevant, assisting the clinician and patient in terms of treatment and prognosis. The ILAE epilepsy syndrome classification, despite all its shortcomings, largely fulfils these requirements. The Cleveland classification, despite its many merits, does not.

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Seizures, syndromes and classifications

Letter to the Editor

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In his most thoughtful editorial commentary Peter Wolf (Wolf 2003) quotes Johns Hughlings Jackson's comparison of a botanist's and a gardener's classification of plants. Jackson differentiated two kinds of classification systems, the scientific and the empirical. As every discussion over classifications, these comments lead directly into the theory of knowledge. For Berg and Blackstone (Berg and Blackstone 2003) a notion of Ax (Ax 1996) represents the heart of effort of classification: "There is a real world that exists independently of our intellectual capacity to understand it." However, under all circumstances we are captured by our experiential and intellectual tools, including the most advanced methodologies and concepts. To summarize Immanuel Kant's Copernican turn: We don't see things as they are, but things are as we see them. Therefore, an absolute knowledge remains an impossible and meaningless abstraction. If we want to classify our experiences – what else should we classify? –, we always have to compromise between the botanist's and the gardener's systems.

Besides the progress in science, changes in classifications are subject to social and political circumstances (Kuhn 1970). A classification needs basic underlying principles and rules. These principles summarize the present knowledge in form of an unquestioned theory or set of beliefs, without an ultimate scientific proof. To speak in the words of Kuhn, the basis of classifications are paradigms. With new scientific observations, information or facts contradicting the prevailing paradigms, additional ad hoc hypotheses may support the leading theories for a substantial time, until this strategy fails or the protagonists of the former dominant paradigm resign. A change of fundamental paradigms occurs in a revolutionary rather than an evolutionary way. Applied to classifications of epileptic seizures and epilepsies, we have to ask ourselves: is it really time for a revolution?

Two major contributions opened the field for a paradigmatic change. The ILAE Commision report (Engel 2001) and the Cleveland proposal (Loddenkemper *et al*. 2005) reorganized the approach to new classifications. Fundamental to both systems are diagnostic axes or dimensions. In contrast to Engel (Engel 2001), who proposed a diagnostic scheme, Loddenkemper *et al*. (2005) speak of a "five-dimensional patient-oriented epilepsy classification". Leaving details aside, both proposals are standardized frameworks for case histories and by no means new classifications. Comparable principles have been used in many institutions for many years and for several medical areas as a modular construction system for diagnostic purposes. To utilize an abridged compilation of relevant data, instead of boiling the details down to a significant single term represents nothing else than a surrender to classification. The complexity of seizures and epileptic syndromes might justify this approach. But there is the danger of losing the ground of previous, admittedly imperfect classifications without a safety net of a new conceptual framework (Avanzini 2003). Engel (Engel 2001) advocates for flexibility and does not exclude the creation of various

classification systems. However, flexibility counteracts the fundamental aim of classifications and provokes a relapse into the private languages of so-called medical schools.

The dichotomy to distinguish between seizure types and epilepsies (Commission on Classification 1981, 1989) was maintained in both new approaches. The y*et al*ready elaborated semiological seizure classification from Lüders *et al*. (1998) is based on a purely descriptive phenomenological approach claiming to be objective and scientific as opposed to the ILAE classification. However, an aura is by definition strictly subjective and many other symptoms and signs are only adequately assessed in the semiologic classification system by adding an additional powerful tool or technique, namely a keen and thorough ictal testing by an experienced "observer". The principles for a proposed new ICES (Engel 2001) consider this approach as an option that can be used in detail where appropriate. Additionally several paradigmatic shifts were announced (Engel 2001). The division of partial seizures into "simple" and "complex" will be abandoned, because this designation should have lost meaningful precision. We do not consider the loss of consciousness a meaningless seizure symptom especially not for the patient. Rather than neglecting this subjective but important symptom, we should properly define "impairment of consciousness" as a combination of reduced reactivity and memory during a seizure. A further paradigmatic shift concerns the elimination of the differentiation between focal and generalized seizure types. Engel correctly argues that seizures as well as syndromes include a variety of diffuse hemispheric, multifocal, and bilaterally symmetrical abnormalities. Nonetheless, a classification according to epileptic networks has yet to be elaborated which could eventually replace a rigid dichotomy focal versus generalized.

Wolf (2003) believes that there is nothing fundamentally wrong concerning the taxonomic principles and system in the 1981 ICES (Commission on Classification 1981). The aforementioned changes probably can be made within the framework of the 1981 ICES. However, as Avanzini (2003) correctly pointed out, the sequence of seizure symptoms is only marginally reflected in the 1981 ICES and also neglected in the ILAE report (Engel 2001). The Cleveland seizure classification (Loddenkemper *et al*. 2005) puts its efforts in documentation of the sequence of seizure symptoms. As with the axes or dimensions, the system represents a check list for symptoms and signs but not a classification of seizures. A mathematical approach to the sequence of seizure symptoms as suggested by some authors is not trivial and most attempts to use cluster analytic methods have been disappointing.

Epilepsy classification is the last step when diagnosing people with epileptic seizures. Since most conditions with chronically recurring epileptic seizures are not properly defined disease entities, we are confined to establish syndromes. Per definitionem, syndromes are nothing else than complexes of symptoms and signs occurring together. Their biological and scientific significance ranges from exactly defined diseases like Unverricht-Lundborg syndrome to unspecific complexes like shoulder-arm syndrome. Lüders *et al*. (2006) emphasize, that most epileptic syndromes have never been defined scientifically, which is implicit in the term syndrome. The hope, that syndromes will be replaced by diseases (morbus) in the near future, seems to be unrealistic despite the vehement scientific progress in different areas. Even the Cleveland classification (Loddenkemper *et al*. 2005) admits the usefulness of some syndromic delineation. It goes by itself, that everybody will be open for the light on the horizon in the form of a perfectly scientific disease classification. If genetic research will bring the answer to all basic questions of taxonomy is highly questionable in face of the genetic heterogeneity on one hand and the phenotypic variability on the other. Therefore, we should use the syndromic classification in a pragmatic way, bearing in mind that it remains a gardener's classification.

Keywords: epilepsy classification, seizure classification, epilepsy genetics, etiology of epilepsies

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