

Revised terminology and concepts for organization of the epilepsies: Report of the Commission on Classification and Terminology

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Introduction: The history of classification has rested largely upon astute observations and expert opinions. First published in 1960 and last updated officially in 1981 for seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) and 1989 for epilepsies (Commission on Classification and Terminology of the International League Against Epilepsy, 1989), the ILAE classifications are based on concepts that, for the most part, predate modern neuroimaging, genomic technologies and concepts in molecular biology. The original authors foresaw that changes to the classification would be needed as new information was acquired and as new investigative technologies were developed. This is no simple task. Attempts have been made to update the 1989 and 1981 documents (Engel J, 2001, 2006); however no new proposal has been forthcoming. During the current Commission's term, input has been sought from experts in the genetics of epilepsy, neuroimaging, therapeutics, pediatric and adult epileptology, as well as statistics and research design. The goal has been to develop a methodologically and conceptually sound and clinically meaningful revision to the classification of the epilepsies and seizures.

In trying to do this, however, we found that the word "classification" has been used to refer to at least three different although related concepts: A. The list of entities that are recognized as distinct forms of epilepsy; B. The concepts and structure underlying the organization and presentation of that list. C. The methods and process that determine which entities are recognized and those features by which those entities are organized.

A. Of particular importance to practitioners, no changes are being made to the list of entities that have been recognized and which was updated in the 2006 Task force report (Engel, 2006). Further, the revisions to be discussed in this document do not have any tangible impact on how clinicians use the diagnostic entities that have been internationally recognized and which are applied to patients everyday around the world.

B. The 1989 classification was not a true scientific classification but rather an organization built on concepts which no longer correspond to or accurately describe our increasing knowledge of seizures and the epilepsies. Consequently, the current organization and the concepts on which it is based are being abandoned or revised. The dimensions by which we characterize seizures and epilepsies should represent useful, natural classes. Further the order and organization of the list of recognized syndromes need not be singular, constrained or rigid but should be flexible to reflect our best current understanding of the neurobiology, the clinical features, prognostic implications, and any other features that are relevant to clinical practice or research.

C. The expert-opinion review process for "admitting" a syndrome to the list will need to be replaced by a system based upon objective analysis using robust statistical methods. This will be required to validate currently accepted syndromes, provide leads for new potential syndromes and to provide some guidance into the natural classes and dimensions by which a scientific classification could be constructed (Berg & Blackstone, 2006). This is a process we intend to initiate in the upcoming years.

In the meanwhile, the Commission has reviewed the current classifications such as they are and made changes to terminology and concepts. Some of this work was greatly aided by proceedings of the Monreale workshop (Capovilla et al. 2009). In what follows, we present a brief summary of those changes followed by a longer explanation of the rationales behind them. Although we set forth a revised and simplified classification for seizures, we do not present a new classification (in the sense of organization) of epilepsies as such. Rather we have provided new terminology and concepts which better reflect the current understanding of these issues. A guiding principle has been to strive for clarity and simplicity so that terms refer to single qualities and are not a mixture of different concepts and dimensions.

Summary of Changes in Terminology and Concepts:

1. Mode of seizure onset and Classification of Seizures (Table 1):

Generalized epileptic seizures are now considered to originate at some point within, and rapidly engage, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another. Generalized seizures can be asymmetric.

Focal epileptic seizures are now considered to originate within networks limited to one hemisphere, which may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures. For each seizure type, ictal onset is consistent from one seizure to another with preferential propagation patterns, which can involve the contralateral hemisphere. In some cases, however, there is more than one epileptogenic network, and more than one seizure type, but each individual seizure type has a consistent site of onset. Focal seizures do not fall into any recognized set of natural classes based on any current understanding of the mechanisms involved.

In a departure from the 1989 classification scheme, syndromes will no longer be characterized as being generalized or focal (“localization-related”).

2. Syndrome versus epilepsy:

The 1989 report used the terms “syndromes” and “epilepsies” almost interchangeably. Henceforth, the use of the term “syndrome” will be restricted to a group of clinical entities that are reliably identified by a cluster of electro-clinical characteristics. Patients whose epilepsy does not fit the criteria for a specific electro-clinical syndrome can be described with respect to a variety of clinically relevant factors (e.g. known etiology, seizure types, etc). This does not, however, provide a precise (syndromic) diagnosis of their epilepsy.

3. Underlying type of cause (etiology)

Underlying causes will be grouped as:

- Genetic*
- Structural/Metabolic*

- *Unknown*

These terms are defined in the accompanying text. They do not entirely correspond to and should not be interpreted as simple substitutions for the older ones.

4. Organization:

In the 1989 publication, syndromes were organized primarily according to “mode” of expression (localization-related versus generalized) and underlying cause (idiopathic, symptomatic, and cryptogenic). We recommend that this approach to classification be abandoned and that, in preparation for the paradigmatic shift in classification, which will be forthcoming, we organize our knowledge regarding syndromes and epilepsies in a flexible, multidimensional manner as appropriate for the specific purpose. An organizational structure which first emphasizes cause, age at onset or virtually any feature (e.g. known channelopathy, specific EEG features, specific types of MRI findings) can thus be constructed.

Explanatory Notes

The previous “classifications” of seizures and epilepsies were often treated as rigid doctrine. This simplified efforts to teach concepts of epilepsy and to perform therapeutic trials. Advances in all areas of investigation (epidemiology, electrophysiology, imaging, developmental neurobiology, genetics, systems neurophysiology, and neurochemistry) have made it clear, however, that such a simple approach does not do justice to the complexity of the underlying developmental and physiological processes. Therefore any classifications put forth by this Commission should be viewed as a guide to summarize our current understanding about seizures and epilepsies in a useful manner, one that is responsive to the needs to which it is put as well as flexible enough to incorporate new information as it develops. The full significance of this will not be apparent until the anticipated new approaches to classification are fully developed. In the interim, we encourage people to begin conceptualizing a future classification as a flexible, multidimensional catalog of essential key features that can be used for organizing information about different forms of epilepsy (or seizures) as appropriate for the purposes of clinical practice, antiepileptic drug development as well as clinical and basic research. It will, in essence, be a database. In the future, those and other essential pieces of information will form the basis for developing a diagnostic manual. The following presents the changes in current conceptualization, terminology, and definitions with the rationales behind these changes.

I. Mode of seizure onset and Classification of Seizures:

The terms ‘focal’ and ‘generalized’ have been used to express a dichotomous classification for both seizures and the epilepsies. For seizures, based on current electro-clinical evidence, such a dichotomy remains useful. However, for epilepsies, recent electro-clinical, imaging and genetic data do not support such a simple dichotomy.

According to current knowledge all epileptic seizures involve neuronal networks, which can be relatively localized, more widely distributed, limited to one hemisphere, or

bilateral. These networks often involve both cortical and subcortical structures. Consequently, the terms ‘focal’ and ‘generalized’ need to be clarified to reflect the current underlying pathophysiology and anatomical substrates of ictal events:

In referring to seizures, focal indicates that the seizures originate primarily within networks limited to one cerebral hemisphere. These may be discretely localized or more widely distributed. Some lesions in subcortical structures may produce focal seizures (e.g. hypothalamic hamartomas). For each seizure type, ictal onset is consistent from one seizure to another with preferential propagation patterns, which can involve the contralateral hemisphere. In some cases, however, there is more than one epileptogenic network, and more than one seizure type, but each individual seizure type has a consistent site of onset. This also applies to cases in which focal seizures may arise independently in either hemisphere (eg bilateral mesial temporal lobe epilepsy or benign epilepsy with central temporal spikes (BECTS)).

Generalized epileptic seizures originate within, and rapidly engage, bilaterally distributed networks. Such bilateral networks can include cortical and subcortical structures, but do not necessarily include the entire cortex. Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another. Generalized seizures can be asymmetric.

In addition, the following specific changes to the 1981 classification of seizures have been made.

1. Neonatal seizures are no longer regarded as a separate entity. Seizures in neonates can be classified within the proposed scheme below.
2. The previous subclassification of absence seizures has been simplified and altered. Myoclonic absence seizures and eyelid myoclonia are now recognized.
3. Epileptic spasms are now included in their own category as seizures which may be generalized, focal, or of unclear onset.
4. Under focal seizures the distinction between the different types (e.g. complex partial and simple partial) is eliminated. It is important however to recognize that impairment of awareness or other dyscognitive features, localization, and progression of ictal events can be of primary importance in the evaluation of individual patients and for specific purposes (e.g. randomized trials, surgery). Nothing in this recommendation precludes describing focal seizures according to these features (see further below).
5. Myoclonic atonic (sometimes referred to as myoclonic astatic) seizures are now recognized
6. The category of unclassified epileptic seizures has been eliminated

The list of recognized generalized seizures may be found in Table 1.

[TABLE 1]

Descriptors of focal seizures The 1981 seizure document used the terms simple partial, complex partial and partial seizures secondarily generalized. This terminology was imprecise as the terms “simple” and “complex” were often misused or

misunderstood. Moreover, the distinction based on impairment of consciousness, although of great pragmatic social importance (eg for driving competence), was impossible to define in a precise scientific manner (Gloor 1986). The term “secondarily” generalized is poorly understood and inconsistently used. At the present time, we do not have the necessary information to create a scientific classification within focal seizures. Regardless, for pragmatic reasons and to facilitate continuity with the 1981 classification of seizures, descriptors of focal seizures may be used, individually or in combination with other features depending on the purpose. For example, in certain circumstances such as pre-surgical evaluation it may be useful to have the sequence of specific elemental features of seizures described (Blume WT et al., 2005, Luders et al., 1993). We have listed descriptors chosen to facilitate continuity with the 1981 seizure document (Table 2). We emphasize, however, that these descriptors do not represent natural classes and are not a “classification” as such.

[TABLE 2]

II Syndromes and Epilepsies:

The 1989 proposal incorporated all forms of epilepsy into an all-encompassing organizational system. The result of this inclusiveness was that the term “syndrome” took on a broad and very imprecise meaning to the point where very specific and highly recognizable entities (such as childhood absence epilepsy) and poorly differentiated and not well described epilepsies (such as cryptogenic parietal lobe epilepsy) tended to be treated as though they represented the same level of diagnostic precision. The result was a veneer of equivalency bestowed upon all epilepsy entities identified within the document. An important revision therefore entails explicitly acknowledging the different levels of specificity and cohesiveness among the various entities that represent different epilepsy diagnoses.

Disease versus syndrome: Although there is reason to distinguish the concepts of disease and syndrome, these terms are not consistently used in medicine. Ultimately, it was decided not to insist on the disease-syndrome distinction in referring to the epilepsies at this time, although either or both terms may be used depending on the context and custom. Instead, there are at least four groupings that may be invoked in this context and as described below:

Electroclinical syndromes: An electroclinical syndrome is a complex of clinical features, signs and symptoms that together define a distinctive, recognizable clinical disorder. These often become the focus of treatment trials as well as of genetic, neuropsychological, and neuroimaging investigations (e.g. Guerrini R et al., 2007, Ottman et al., 2008, Scheffer IE et al., 1998, Scheffer IE et al., 2008)).

Use of the term “syndrome,” and more precisely “electro-clinical syndrome,” will be restricted to a group of clinical entities that are reliably identified by a cluster of electro-clinical and developmental characteristics. These are largely but not exclusively genetic in origin, and tend to have a strong relationship to developmental aspects of the brain. These are distinctive disorders identifiable on the basis of a typical age onset, specific EEG characteristics, seizure types, and often other features which, when taken

together, permit a specific diagnosis. The diagnosis in turn often has implications for treatment, management, and prognosis. The term for these entities is “*Electro-clinical Syndromes*.” While ultimately common usage will likely shorten the term again to “syndrome” alone, this is still specifically defined to mean entities that can be considered *electro-clinical syndromes*. It would be inappropriate to refer to, for example, epilepsy with a frontal lobe focus and not otherwise specified as a “syndrome.” The currently recognized electro-clinical syndromes are presented in the first part of Table 3 organized by typical age at onset as this is one of the most distinctive and clinically salient dimensions for organizing these entities.

Constellations: In addition to these electro-clinical syndromes, there are a number of entities that are not recognized as electro-clinical syndromes *per se* but which represent clinically distinctive *constellations* on the basis of specific lesions or other causes. These are diagnostically meaningful forms of epilepsy and may have implications for clinical treatment, particularly surgery. Chief among these are Mesial Temporal Lobe Epilepsy (with hippocampal sclerosis), hypothalamic hamartoma with gelastic seizures, and Rasmussen “syndrome.” Age at presentation is not a defining feature in these disorders, as we understand them.

Epilepsies secondary to specific structural or metabolic lesions or conditions: The next group includes epilepsies secondary to specific *structural or metabolic lesions or conditions* but which do not, given our current understanding, fit a specific electro-clinical pattern, although that may change in the future. Therefore, these entities represent a lower level of specificity than the two previous groups. In the past, many such epilepsies were grouped together as “symptomatic focal epilepsies” and largely distinguished on the basis of localization. In the revised classification, we recommend that less emphasis be given to localization and more to the underlying structural or metabolic cause. Consequently, terms such as “symptomatic temporal lobe epilepsy” are replaced by longer but more precise expressions such as “epilepsy with focal seizures secondary to focal cortical dysplasia in the temporal lobe.” Localization may be considered but is not, based on our current knowledge, the primary factor of importance for understanding the cause and prognosis of the epilepsy. These epilepsies are now included in the over-arching etiological grouping of “*Structural /metabolic epilepsies*.” (see below)

Epilepsies of unknown cause: What remains are those epilepsies which in the past were termed “cryptogenic,” including those that were considered “undetermined.” These epilepsies account for a third or more of all people with epilepsy, are the most poorly understood and represent perhaps the most fertile area for future research in imaging and genetics. For such research to be feasible, however, it will require that the simple characterization by localization of inter-ictal spike (e.g. cryptogenic parietal lobe epilepsy) be replaced with a detailed characterization of all relevant features (e.g. age at onset, specific EEG features, cognitive and developmental assessments, diurnal patterns of seizure occurrence, etc). Among these poorly differentiated epilepsies are likely to be additional genetic electroclinical syndromes; however, they cannot be recognized until they are adequately characterized. Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) and autosomal dominant partial epilepsy with auditory features (ADPEAF)

are examples of specific electro-clinical syndromes which were discovered within these poorly differentiated epilepsies (Ottman R et al., 1999, Scheffer et al., 1995). This approach will also facilitate identification of non-genetic determinants of epilepsy. The label for this group in which no cause has yet been identified is “*epilepsies of unknown cause.*”

Table 3 provides a list of entities according to their level of specificity and within those designations, by age at onset where meaningful.

[TABLE 3]

Note that in referring to syndromes the dichotomy of focal versus generalized will be abandoned, ie. “the focal or generalized epilepsies.” Instead epilepsies will be referred to according to the etiological designation and further as characterized by seizures of generalized or focal onset or both. This is meant to separate the manifestations from the pathophysiology.

III. Etiological Designation:

The terms idiopathic, symptomatic, and cryptogenic have taken on a variety of meanings and connotations laden with presumptions which, at times, conflate multiple concepts into a single word. This has resulted in considerable contradiction and confusion. The term idiopathic was defined in the 1989 document: “*There is no underlying cause other than a possible hereditary predisposition. Idiopathic epilepsies are defined by age-related onset, clinical and electrographic characteristics, and a presumed genetic etiology.*” The term, however, is also used to convey the idea of a highly pharmaco-responsive form of epilepsy. Many, although not all, of the traditional “idiopathic” epilepsies also spontaneously remit during a predictable age range (a separate quality or dimension) and were generally thought to be unaccompanied by other consequences or disabilities, although this is clearly not the case as a variety of subtle cognitive and behavioral disorders are seen in association with these forms of epilepsies.

The term “symptomatic” is a truism as all epilepsy is symptomatic of something. It is often substituted for the concept of a poor prognosis for seizure control. Finally, “cryptogenic” was defined in 1989 as meaning “presumed symptomatic” apparently in the sense of “lesional.” It is, however, from among these “cryptogenic” epilepsies that syndromes such as ADNFLE and ADPEAF have been discovered. The Commission has abandoned all three terms and redefined concepts for groups of underlying cause.

The following three groups for causes are recognized:

1. *Genetic.* The concept of genetic epilepsy is that *the epilepsy is, as best as understood, the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder.* The knowledge regarding the genetic contributions may derive from specific molecular genetic studies that have been well replicated and even become the basis of diagnostic tests (e.g. *SCN1A* and Dravet syndrome) or the central role of a genetic component may rely on evidence from appropriately designed family studies. Designation of the fundamental nature of the disorder as being genetic

does **not** exclude the possibility that environmental factors (outside the individual) may contribute to the expression of disease. At the present time, there is virtually no knowledge to support specific environmental influences as causes of or contributors to these forms of epilepsy. Examples of epilepsy syndromes that would be classified as genetic epilepsies include childhood absence epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, and Dravet syndrome. Note that in the 1989 classification, Dravet syndrome was not classified as idiopathic epilepsy. It will now be considered as a genetic epilepsy. In doing this, we are requiring the concept of cause to contain only one dimension and not include multiple factors such as treatment response, likelihood of spontaneous remission, or severity of consequences and co-morbid conditions. Cause is no longer equated with prognosis, and the implication that “idiopathic” implies “benign” is intentionally discarded. It is possible that the genetic defect may have other effects in addition to the seizures but, as best we can tell, these other effects are not interposed between the genetic effect and the seizures.

2. “*Structural/metabolic.*” The concept of a grouping together structural and metabolic causes of epilepsy is that there is a distinct other condition or disease that has been demonstrated to be associated with a substantially increased risk of developing epilepsy in appropriately designed studies. Structural lesions of course include acquired disorders such as stroke, trauma, and infection. They may, however, also be of genetic origin (e.g. tuberous sclerosis, many malformations of cortical development). The distinction is that there is a separate disorder that appears to be interposed between the genetic defect and the epilepsy.

The Commission acknowledges that as new genetic contributions to epilepsy are recognized, it may often be difficult to know how best to characterize them with respect to the distinctions above. For example, *ARX*, a homeobox gene, is associated with phenotypic heterogeneity including West syndrome and lissencephaly (Stromme et al, 2002). *STXBPI* encodes a protein involved in synaptic vesicle release and is associated with Ohtahara syndrome (Saitou et al., 2008). Both syndromes involve severe encephalopathic forms of epilepsy. In the first case, one might conceivably consider the *ARX* mutation in the structural/metabolic category. In the case of *STXBPI*, because of the function of the protein product, one might possibly associate this with the concept of genetic epilepsy. No determination has been made in either case at this time. Instead the role of the specific genetic error should be recognized but it is not necessary to pigeon-hole the cause of the disorder further unless there is an adequate basis for doing so. We advocate a focus on mechanisms. This focus will ultimately reveal the natural classes. The overly simplistic designation of “genetic” versus “structural-metabolic” will then be replaced by a more precise characterization of the underlying cause. Groups and names for groups of causes should ultimately reflect natural classes.

3. “*Unknown cause.*” Unknown is meant to be taken neutrally and to designate that the nature of the underlying cause is as yet unknown, it may have a fundamental genetic defect at its core or it may be the consequence of a separate disorder or condition not yet recognized. Examples of syndromes that would be classified as “of unknown cause” include migrating partial seizures of infancy and myoclonic epilepsy in infancy (formerly benign myoclonic epilepsy of infancy, (Engel J, 2006)). At the present time, it might be

reasonable to include some of the traditional “idiopathic” electro-clinical syndromes in this category as well. These include benign rolandic epilepsy (Vadlamudi L. et al., 2006) and the benign occipital epilepsies of childhood, both Panayiotopoulos and Gastaut types (Taylor I, et al., 2008). It is likely that genetic factors are involved in these syndromes but present evidence (e.g. low or absent concordance in siblings) does not suggest that genetic factors are paramount.

Certain electro-clinical syndromes, such as infantile spasms, may have multiple different causes. This should be acknowledged when describing the syndrome in general, and the specific cause should be identified for the individual patient.

IV. Other dimensions for classifying epilepsies and organizing information:

In addition to the traditional dimensions and features, each syndrome and each patient can be characterized according to a large number of other features which are often routinely part of any patient’s evaluation and which are essential features in distinguishing among established syndromes. These include the cognitive and developmental antecedents and consequences, motor and sensory exam, EEG features, provoking or triggering factors, patterns of seizure occurrence with respect to sleep. In addition, there are two traditional clusters of syndromes which, for the present, are convenient to maintain, “idiopathic generalized epilepsy syndromes” and “idiopathic focal epilepsy syndromes.” The significance and validity of these groupings may be upheld or ultimately rejected in time. The use of the term “idiopathic” in this context is anachronistic and vestigial much as is the expression “to dial” a phone number is used in most parts of the world today.

IV- A. Age at onset: For the purposes of grouping syndromes or individuals, age at onset categories are recommended as per standard use: neonate (<44 weeks gestational age), infant (<2 years), child (2-12 years), adolescent (12-18 years), and adult (>18 years). The age ranges are approximate and meant to be used only for convenience in describing already characterized forms of epilepsy. For individual patients, the exact age at onset or best approximation should be used, and greater precision for syndromes is encouraged when possible.

IV- B. Natural evolution: Many terms have crept into usage to describe the natural course and consequences of epilepsy. These terms include “epileptic encephalopathy” and “benign.”

1. **Epileptic encephalopathy.** The concept of epileptic encephalopathy embodies the notion that the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology (e.g. cortical malformation) alone, and that these can worsen over time. Inherent in this concept is the idea that by suppressing or preventing the epileptic activity, one may improve the cognitive and behavioral outlook of the disorder. In the developing brain, this concept has led to the hope that rapid effective intervention should and can be used before the abnormal epileptic activity interferes irrevocably with normal processes

of brain development. Recent studies in children from the surgical and pharmacological literature (Freitag H and Tuxhorn I, 2005, Jonas R et al., 2005, Jonas R et al., 2004, Lux AL et al., 2005) tend to support this concept. Epileptic encephalopathy can present along a continuum of severity and may occur at any age. The phenomenon is most common and severe in infancy and early childhood where global and profound cognitive impairment may occur. Adults, however, can also suffer cognitive losses over time from uncontrolled seizures (Hermann B., et al. 2006).

The term “epileptic encephalopathy” can be used to characterize syndromes as well as be applied to individuals. As a *domain for clustering and describing syndromes*, an epileptic encephalopathy is an electro-clinical syndrome associated with a very high probability that the individual will develop encephalopathic features that present or worsen after the onset of epilepsy. Separately but important to note, as a group they tend to be very pharmaco-resistant but this is another quality or dimension. The best known and most common of these are West, Lennox-Gastaut, Dravet, Landau-Kleffner-CSWS, and Doose syndromes. Inclusion of a specific syndrome in the domain of “epileptic encephalopathy” does not imply that all individuals with these disorders will appear encephalopathic; however the risk is typically quite high. Recognition of this risk is a primary motivation for creating this domain as early effective intervention including surgery may improve seizure control and developmental outcome in some cases. *Diagnosing an individual* as having an encephalopathic course requires demonstration of a failure to develop as expected relative to same-aged peers or to regress in abilities. Note that it is not necessary for an individual to have a syndrome identified as being one of the “epileptic encephalopathies” in order to have an encephalopathic course.

“Epileptic encephalopathy” should be viewed as a concept and a description of what is observed clinically with the recognition that, we are rapidly approaching a clearer understanding of the effects of seizures on brain function and their potential for lasting deleterious impact in the developing brain. At the same time, however, we must recognize that the source of an apparent encephalopathy is usually unknown. It may be the product of the underlying cause, the result of epileptic activity, or a combination of both.

2. “Benign”: The names of many syndromes contain the word “benign.” Two key features of “benign” epilepsy syndromes are that they:

a. Involve seizures which are self-limited in that spontaneous remission, regardless of treatment, occurs at an expected age and is the anticipated outcome in the vast majority of cases,

b. The consequences, if any, of the seizures are generally not disabling over the course of the active seizure disorder. This does not preclude an increased risk of subtle to moderate cognitive and behavioral disorders prior to, during, or extending beyond the active phase of the seizures.

With our increasing awareness, however, of the cognitive and behavioral comorbidities, psychiatric disorders, migraine, and even sudden death that may

accompany any form of epilepsy, the term “benign” itself seems inappropriate as it may lead to false hopes and unrealistic expectations.

As did the term “idiopathic,” “benign” blends together different qualities which, individually, may pertain to other epilepsies that are not considered “benign.” Consequently, we recommend that, instead of designating a group of syndromes as “benign,” we recognize the different qualities that make up the concept of benign and apply them specifically and consistently to individual forms of epilepsy. While predictable spontaneous remission is a desirable quality, it should be identified as “self-limited” electro-clinical syndromes, that is, electro-clinical syndromes that have a high or moderately likelihood of spontaneously remitting at a predictable age.

Another feature that is also seen in these self-limited syndromes is that they are also very pharmaco-responsive. This is true of other syndromes that are not always as self-limited such as CAE and JME. Diagnosis of one of these syndromes allows, within a reasonable certainty, the prediction that the seizures will rapidly come under control with appropriate medication. In fact, this is one of the common features of the groups of syndromes previously labeled “Idiopathic.” Diagnosis of one of these electro-clinical syndromes is of key importance for family and patient counseling. Labeling these syndromes as pharmaco-responsive is likely more meaningful to clinicians and families than the term “idiopathic” which contains other implications which may or may not apply to a given electroclinical syndrome.

Of note, the inclusion of features that are descriptive of the natural evolution of a form of epilepsy is not, strictly speaking based upon natural classes but rather on repeated observations and impressions. They are included for pragmatic purposes.

IV-C. Other features: Many other dimensions and features will ultimately be used in describing, classifying, and grouping the different forms of epilepsies. Depending on the purpose, these other features may be more useful in grouping and organizing syndromes and forms of epilepsy than are the primary ones with which most of us are familiar. Dimensions would include but are not limited to detailed aspects of ictal and interictal EEG, structural neuroimaging findings, neurological exam, cognitive and psychiatric status

An interim organization (“classification”) of the epilepsies:

In a departure from the 1989 classification of the epilepsies, there is no one specific organization proposed for the revised classification. Instead, the various forms of epilepsy (at all levels of specificity) will be organized according to whichever dimensions are most relevant to a specific purpose. These may be essentially the same dimensions used in the 1989 classification (mode of seizure onset, “etiology” and age at onset) a different hierarchical arrangement of these same dimensions, a more detailed version of these dimensions, or by an entirely different set of dimensions, as appropriate to the purpose. For example, rather than a simple dichotomy of epilepsies based on association with focal versus generalized onset seizures, epilepsies can be organized by specific seizure type. The advantages of this from the perspective of a future diagnostic manual are considerable. Epilepsies could also be organized by specific cause, e.g. ion

channelopathies and within that category, specific ion channel genes, as is being done with prolonged QT syndrome (Johnson et al., 2008). By the same token one could organize a subgroup of epilepsies according to age at onset and association with *specific* types of malformations of cortical development (e.g. see Lerner et al. 2009).

The benefits of this approach become increasingly clear as one considers the differences between characterizing and classifying syndromes versus individual patients. A syndrome is characterized with respect to a host of factors. If one knows a given patient's syndromic diagnosis, one knows a considerable amount about that patient's epilepsy, e.g. likely age at onset, EEG patterns, likely responses to medications, cognitive and developmental status, and so forth. We can organize our information about these syndromes along the many dimensions by which they are characterized. For those epilepsies that do not fall into clear electro-clinical syndromes and which are associated with structural-metabolic causes, the most natural and rational primary approach to classifying or organizing them is by the specific underlying cause or lesion. For those epilepsies of unknown cause and that are predominately characterized by mode of seizure onset, there is no natural class that conveniently and validly sorts them into more homogeneous groups. The revised recommended approach explicitly acknowledges this. Forcing these partially or poorly characterized epilepsies into a system of classification for which they are not yet ready suggests greater knowledge than we currently have and serves to impede progress. Much greater effort should be invested, both in the clinic and in clinical research, into characterizing individual patients in sufficient detail according to such a set of dimensions and in such a way as to facilitate objective research into identifying previously unrecognized constellations and syndromes. This information can then be used as the basis for objective analyses to identify potential new "syndromes" (Berg and Blackstone, 2006). It will also greatly facilitate the use of the planned diagnostic manual which will provide a guide with specific definitions and examples that will encourage clinicians to make the necessary observations on all patients in order to make or exclude specific diagnoses.

This report updates the current terminology and concepts in classification of epilepsy until a completely different set of methods can be put in place. The plans for that process will be described in detail separately. For the new approach to be successful, however, broad consensus and input from the epilepsy community will be required at each step of the way. We encourage all those to whom this is of interest carefully to consider the issues raised above, to follow future announcements and reports, and to participate in the discussions to ensue. For now, we remind everyone that (1) any classification approach should be viewed as summarizing our current level of knowledge and not as a rigid, final document and (2) the classification maintain its primary clinical value for understanding, diagnosing, and treating epilepsy. Finally, in terms of impact on the clinical use of the diagnostic entities that are listed in the previous ILAE statements, there is none. No changes have been made to the list of epilepsies, and the list of seizure types, while simplified, is not substantially different although we hope it will lead to less confusion and error in its application. In sum, we should all be as specific and precise as possible about each patient's type of epilepsy, seizures, and underlying cause.

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- Berg AT, Blackstone NW. (2006) Concepts in classification and their relevance to epilepsy. *Epilepsy Res* 70:11-19
- Blume WT, Luders HO, Mizrahi E, Tassinari C, van Emde Boas W and Engel J (2005) International League Against Epilepsy.
- Capovilla G, Berg AT, Cross JH, Moshe SL, Vigeveno F, Wolf P, Avanzini G. (in press) Conceptual dichotomies in classifying epilepsies: Partial versus generalized and idiopathic versus symptomatic (April 18-20, 2008, Monreale, Italy). *Epilepsia*.
- Capovilla G, Berg AT, Cross JH, Moshe SL, Vigeveno F, Wolf P, Avanzini G. Conceptual dichotomies in classifying epilepsies: partial versus generalized and idiopathic versus symptomatic (April 18-20th, 2008, Monreale, Italy) *Epilepsia* 2009;50:1645-1649.
- Commission on Classification and Terminology of the International League Against Epilepsy (1981) Proposal for revised clinical and electrographic classification of epileptic seizures. *Epilepsia*. **22**: 489-501.
- Commission on Classification and Terminology of the International League Against Epilepsy (1989) Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. **30**: 389-399.
- Engel J (2001) A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia*. **42**: 796-803.
- Engel J (2006) Report of the ILAE Classification Core Group. *Epilepsia*. **47**: 1558-1568.
- Freitag H and Tuxhorn I (2005) Cognitive Function in Preschool Children after Epilepsy Surgery: Rationale for Early Intervention. *Epilepsia*. **46**: 561-567.
- Gloor P (1986) Consciousness as a neurological concept in epileptology: a critical review. *Epilepsia* **27**:(Suppl. 2):S14-S26.
- Guerrini R, Moro F, Kato M, Barkovich AJ, Shiihara T, McShane MA, Hurst J, Loi M, Tohyama J, Norci V, Hayasaka K, Kang UJ, Das S, Dobyns WB. (2007) Expansion of the first PolyA tract of ARX causes infantile spasms and status dystonicus. *Neurology* **69**:427-433.
- Johnsons JN, Hofman N, Haglund CM, Cascino GD, Wilde AAM, Ackerman MJ. (2008 epub ahead of print) Identification of a possible pathogenic link between congenital long QT syndrome and epilepsy. *Neurology*.
- Hermann BP, Seidenberg M, Dow C, Jones J, Rutecki P, Bhattacharya A, Bell B. (2006). Cognitive prognosis in chronic temporal lobe epilepsy." *Ann Neurol* **60**: 80-87
- Jonas R, Asarnow RF, LoPresti C, Yudovin S, Koh S, Wu JY, Sankar R, Shields WD, Vinters HV and Mathern GW (2005) Surgery for symptomatic infant-onset epileptic encephalopathy with and without infantile spasms. *Neurology*. **64**: 746-750.
- Jonas R, Nguyen S, Hu B, Asarnow RF, LoPresti C, Curtiss S, de Bode S, Yudovin S, Shields WD, Vinters HV and Mathern GW (2004) Cerebral hemispherectomy: Hospital course, seizure, developmental, language, and motor outcomes. *Neurology*. **62**: 1712-1721.
- Lerner JT, Salamon N, Hauptman JS, Velasco TR, Hemb M, Wu JY, Sankar R, Shields WD, Engel J, Fried I, Cepeda C, Andre VM, Levine MS, Miyata H, Yong WH, Vinters HV, Mathern GW. (2009) Assessment of surgical outcomes for mild type I and severe type II cortical dysplasia: A critical review and the UCLA experience. *Epilepsia* (epub).

- Luders, H O, Burgess, R and Noachtar, S (1993) Expanding the international classification of seizures to provide localization information. *Neurology*. **43**: 1650-1655.
- Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, O'Callaghan FJ, Verity CM and Osborne JP (2005) The United Kingdom Infantile Spasms Study (UKISS) comparing hormone treatment with vigabatrin on developmental and epilepsy outcomes to age 14 months: a multicentre randomised trial. *Lancet Neurology*. **4**: 712-717.
- Ottman R, Barker-Cummings C, Lee JH and Ranta S (1999) In *Genetics of focal epilepsies*. (Eds, Berkovic SF, Genton P, Hirsch E and Picard F) John Libbey & Co Ltd, London, pp. 95-102.
- Ottman, R, Rosenberger, L, Bagic, A, Kamberakis, K, Ritzl, E K, Wohlschlagler, A M, Shamim, S, Sato, S, Liew, C, Gaillard, W D, Wiggs, E, Berl, M M, Reeves-Tyer, P, Baker, E H, Butman, J A and Theodore, W H (2008) Altered language processing in autosomal dominant partial epilepsy with auditory features. *Neurology*. **71**: 1973-1980.
- Saitsu, H, Kato, M, Mizuguchi, T, Hamada, K, Osaka, H, Tohyama, J, Uruno, K, Kumada, S, Nishiyama, K, Nishimura, A, Okada, I, Yoshimura, Y, Hirai, S-i, Kumada, T, Hayasaka, K, Fukuda, A, Ogata, K and Matsumoto, N (2008) De novo mutations in the gene encoding STXBP1 (MUNC18-1) cause early infantile epileptic encephalopathy. *Nat Genet*. **40**: 782-788.
- Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, Andermann E, Andermann F, Desbiens R, Keene D, Cendes F, Manson JI, Constantinou JEC, McIntosh A, Berkovic SF. Autosomal dominant nocturnal frontal lobe epilepsy: A distinctive clinical disorder. *Brain* 1995;118:61-73
- Scheffer IE, Phillips HA, O'Brien CE, Saling MM, Wrennall JA, Wallace RH, Mulley JC and Berkovic SF (1998) Familial partial epilepsy with variable foci: A new partial epilepsy syndrome with suggestion of linkage to chromosome 2. *Annals of Neurology*. **44**: 890-899.
- Scheffer IE, Turner SJ, Dibbens LM, Bayly MA, Friend K, Hodgson B, Burrows L, Shaw M, Wei C, Ullmann R, Ropers H-H, Szepetowski P, Haan E, Mazarib A, Afawi Z, Neufeld MY, Andrews PI, Wallace G, Kivity S, Lev D, Lerman-Sagie T, Derry CP, Korczyn AD, Geicz J, Mulley JC and Berkovic SF (2008) Epilepsy and mental retardation limited to females: an under-recognized disorder. *Brain*. **131**: 918-927.
- Stromme P, Mangelsdorf ME, Shaw MA, Lower KM, Lewis SM, Bruyere H, Lutchterath V, Gedeon AK, Wallace RH, Scheffer IE, Turner G, Partington M, Frints SG, Fryns JP, Sutherland GR, Mulley JC, Geicz J. (2002) Mutations in the human ortholog of *Aristaless* cause X-linked mental retardation and epilepsy. *Nat Genet* 30:441-445.
- Taylor I, Berkovic SF, Kivity S and Scheffer IE (2008) Benign occipital epilepsies of childhood: clinical features and genetics. *Brain*. **131**: 2287-2294.
- Vadlamudi I, Kjeldsen MJ, Corey LA, Solaas MH, Friis ML, Pellock JM, Nakken KO, Milne RL, Scheffer IE, Harvey SA, Hopper JL, Berkovic SF. (2006) Analyzing the etiology of benign rolandic epilepsy: a multicenter twin collaboration. *Epilepsia*. **47**: 550-555.

Table 1: Classification of seizures

GENERALIZED SEIZURES

Tonic clonic (in any combination)

Absence * Typical
 * Atypical
 * Absence with special features
 Myoclonic absence
 Eyelid myoclonia

Myoclonic * Myoclonic
 * Myoclonic atonic
 * Myoclonic tonic

Clonic

Tonic

Atonic

FOCAL SEIZURES

MAY BE FOCAL, GENERALIZED, OR UNCLEAR

Epileptic spasms

Table 2: Descriptors of focal seizures according to degree of impairment during seizure

↳

- * Without impairment of consciousness/responsiveness
 - + With observable motor or autonomic components (roughly corresponds to the concept of “simple partial seizure)
 - + Involving subjective sensory or psychic phenomena only (corresponds to the concept of aura)
- * With impairment of consciousness/responsiveness (roughly corresponds to the concept of complex partial seizure)
- * Evolving to a bilateral, convulsive seizure (involving tonic, clonic or tonic and clonic components; replaces the term secondarily generalized seizure)

Table 3: Electro-clinical syndromes and other epilepsies**Electro-clinical syndromes arranged by age at onset ***

Neonatal period

- Benign familial neonatal seizures (BFNS)
- Early myoclonic encephalopathy (EME)
- Ohtahara syndrome

Infancy

- Migrating partial seizures of infancy
- West syndrome
- Myoclonic epilepsy in infancy (MEI)
- Benign infantile seizures
- Benign familial infantile seizures
- Dravet syndrome
- Myoclonic encephalopathy in nonprogressive disorders

Childhood

- Febrile seizures plus (FS+) (can start in infancy)
- Early onset benign childhood occipital epilepsy (Panayiotopoulos type)
- Epilepsy with myoclonic atonic (previously astatic) seizures
- Benign epilepsy with centrotemporal spikes (BECTS)
- Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)
- Late onset childhood occipital epilepsy (Gastaut type)
- Epilepsy with myoclonic absences
- Lennox-Gastaut syndrome
- Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) including: Landau-Kleffner syndrome (LKS)
- Childhood absence epilepsy (CAE)

Adolescence - Adult

- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic-clonic seizures alone
- Progressive myoclonus epilepsies (PME)
- Autosomal dominant partial epilepsy with auditory features (ADPEAF)
- Other familial temporal lobe epilepsies

Less Specific Age Relationship *

- Familial focal epilepsy with variable foci (childhood to adult)
- Reflex epilepsies

Distinctive Constellations

- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma

Epilepsies that *do not* fit into any of these diagnostic categories can be distinguished first on the basis of the presence or absence of a known structural or metabolic condition

(presumed cause) and then on the basis of the primary mode of seizure onset (generalized versus focal).

Epilepsies attributed to and organized by structural-metabolic causes

Malformations of Cortical development (hemimeganencephaly, heterotopias etc)

Neurocutaneous syndromes (Tuberous sclerosis complex, Sturge-Weber, etc)

Tumor

Infection

Trauma

Angioma

Peri-natal insults

Stroke

Etc.

Epilepsies of unknown cause

Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy *per se*.

Benign neonatal seizures (BNS)

Febrile seizures (FS)

*This arrangement does not reflect etiology.