The ILAE Classification of Seizures and Epilepsies: Implications for the Clinic

Abstract

Introduction: The classification of epileptic seizures and the epilepsies has recently been revised by the International League Against Epilepsy (ILAE) and a new classification scheme issued. **Areas covered**: The new classification scheme has been critically appraised in the light of the previous classifications and subsequent revisions. The purposes of the classification and its potential use have been extensively discussed. **Expert Commentary**: This ILAE classification scheme, the latest of a series of proposals published in the last thirty years, has made progress as it has a multi-level structure (seizure types, epilepsy types, epilepsy syndromes) allowing for differing uses and combines the previously separate seizure types and epilepsies schemes into a single instrument. Seizures and epilepsies can also be classified based on the available diagnostic aids, which may differ substantially between counties with mature economies and resource-poor countries. An intrinsic limitation of the classification, however, is the attempt to box cases as seen in clinical practice into schematic categories, leaving no room for variants and atypical clinical presentations. Another limitation is the lack of flexibility which hampers the ability to link the instrument to the preceding classifications in order to preserve continuity and monitor disease trends in time and space.

Keywords: Epilepsy, classification, clinicians, health care planners, researchers, multi-level stratification.

The Commission for Classification and Terminology of the International League Against Epilepsy (ILAE) has recently published two position papers focusing on the classification of seizure types [1] and the classification of the epilepsies [2]. These reports are an attempt to update, in the light of advancing scientific knowledge, the classifications of epileptic seizures [3] and the epilepsies [4] first released in the 1980s but still in use. It is generally accepted that a classification scheme must follow changes in knowledge of the underlying disease genotypes and phenotypes, but it must be acknowledged that change in the classification scheme has implications for clinical use in terms of understanding, acceptance, ease of use, and application. These implications are some of the reasons why almost three decades elapsed before a new classification scheme was released. Here we discuss the main problems underlying the development of a classification of seizures and epilepsies and how these problems should be addressed so that the classification scheme can be accepted by all users.

The purposes of a scientific classification

A scientific classification scheme is created for the purpose of identifying similar individuals or items as members of a natural class [5]. Based on the way a disease in an individual is classified, generalisations and predictions can be made about that individual. At the same time, categories of disease are identified that are essentially the same and can be distinguished from categories that are different. These biological requirements are the fundamental basis of improving our knowledge of the spectrum of a disease, including epilepsy, in terms of aetiology, natural history and response to the available treatments. For this reason, pathophysiology must be a cornerstone of taxonomy. Such a perspective might, however, confound a classification scheme and turned it unfeasible in practice. In fact, when a classification is used in the clinic, several practical implications arise depending on its use by different stakeholders and on the interpretation of the whole in the light of what is

actually available in clinical practice in terms of investigations.

The users of the classification

The classification of the epilepsies should be, as for any disease, a valid and reliable instrument for the benefit of different users. Practising physicians should find the classification scheme a useful tool for the diagnosis and treatment of the disease and for communication with others using the same language. For health care providers, the scheme should be useful for a comprehensive

assessment of the burden of the disease. Researchers should find the classification a pragmatic instrument for investigating aetiology, underlying pathogenic mechanisms, treatment, and outcome of the disease. In this respect, the classification scheme must fulfil differing and sometimes contrasting needs. The picture is complicated by advancing knowledge as well as by the availability of diagnostic and therapeutic resources at the local level. The historical evolution of the classification of epileptic seizures and the epilepsies reflects the need to satisfy these needs with a single instrument.

Historical background

The first proposal for an international classification of epileptic seizures goes back to 1969 [6,7]. The 1970 epilepsy classification scheme was based on clinical and EEG criteria which were used to classify generalised and focal epilepsies as separate nosographical entities. These criteria were incorporated in the first ILAE classification [7] which included, along with seizures types and interictal electrographic findings, anatomical substrate, aetiology and age. With the advent of video-EEG recording, the classification of seizures was revised, based only on clinical, ictal and interictal EEG findings [3], while age, aetiology (defined as idiopathic, symptomatic or cryptogenic) and anatomical substrate were placed in the forthcoming classification of the epilepsies, issued in 1989

[4]. In the 1989 ILAE classification of the epilepsies the concept of electroclinical syndrome was introduced and defined as a complex of symptoms and signs including age of onset of seizures, seizure type(s), interictal EEG, aetiology and comorbidities, and genetic basis. Since then, several unsuccessful attempts have been made to update the classification of seizures and epilepsies and, at the same time, to adapt it to the needs of different users [8-11].

With this background, the ILAE Commission on Classification and Terminology revised concepts, terminology and approaches for classifying seizures and epilepsies in the light of available knowledge [12]. Generalised and focal seizures were redefined. Generalised seizures were defined as seizures occurring in, and rapidly engaging, bilaterally distributed networks while focal seizures were seizures with onset within networks limited to one hemisphere and either discretely localised or more widely distributed. In non-syndromic epilepsies, the classification of generalised seizures was simplified while focal seizures were described according to their manifestations. The terms genetic, structural–metabolic and unknown were introduced to replace idiopathic, symptomatic, and cryptogenic. Epilepsies were organized in three major categories: electroclinical syndromes, non-syndromic epilepsies with structural–metabolic causes, and epilepsies of unknown cause. Flexibility was introduced to permit the classification of the epilepsies in natural classes or

pragmatic groupings according to the different needs of the users and the technology at hand in the local settings. To enable the adoption of the classification by users with limited resources or insufficient information available, an overarching framework was later developed [13] to allow diagnosis at multiple levels. In this classification scheme, clinicians must first determine whether a paroxysmal event is an epileptic seizure. The diagnosis of seizure type follows according to a revised classification of seizures [1]. At the next level, where possible, a diagnosis of epilepsy syndrome is made. The fourth level of diagnosis establishes the primary aetiology of epilepsy.

Classification and methods of investigation

The structure of a classification of a disease reflects the underlying methods of investigation. Hughlings Jackson elegantly pointed out: "*There are two ways of investigating diseases, and two kinds of classification corresponding thereto, the empirical and the scientific. The former is to be illustrated by the way in which a gardener classifies plants, the latter by the way in which a botanist classifies them. The former is, strictly speaking, only an arrangement. The gardener arranges his plants as they are fit for food, for ornament, etc. One of his classifications of ornamental plants is into trees, shrubs, and flowers. His object is the direct application of knowledge to utilitarian purposes. It is, so to speak, practical. The other kind of classification (the classification properly so-called) is rather for the better organization of existing knowledge, and for discovering the relations of new facts; its principles are methodical guides to further investigation. It is of great utilitarian value, but not directly.*" [14] These empirical and scientific fundaments of any classification have been the object of an intense discussion mainly focusing, even from differing points of view, on the dichotomy between the biological and the clinical significance of the ILAE classification as revised in 2001 [15]. The scientific purposes of a disease classification scheme cannot be disentangled from its practical purposes but two major questions must always be addressed: 1. How to delineate boundaries between what is normal and what is pathologic; 2. How to classify the signs and symptoms in different categories of a disorder [16]. Boundaries between normal and abnormal are often difficult to delineate and are sometimes subject to convenience and non-medical interests. The classification of symptoms and signs in different categories reflects the advancement of the existing knowledge and the evidence base on which an association is interpreted as factual and not casual.

Advantages of the new ILAE classification

A major advantage of the present classification scheme is the use of a multilevel structure which allows differing uses but, most importantly, combines seizure types and epilepsies in a single

instrument. Another advantage is the possibility of classifying seizures and epilepsies on the basis of the available diagnostic aids, which may differ substantially between countries and regions. A valuable addition is the development of an instruction manual for the definition of seizure types [17] that not only offers a glossary of terms to help with the correct use of definitions but also favours a standardisation of the present terminology.

The classification may still have problems

Even with the use of flexible diagnostic categories, any attempt at changing the previous classification schemes has a number of inevitable limitations when used in clinical practice. These limitations are often inherent in the structure of a classification and also a reflection of the application of the scheme by a heterogeneous population of users in terms of background, interpretation of the available findings, and use of the diagnostic categories. The first and perhaps most important limitation is an attempt to label cases as seen in clinical practice into schematic categories (an intrinsic limitation of the classification) which leave no room for disease variants and atypical clinical pictures. It is commonly accepted that, after the first recognition of a given epilepsy syndrome, an increasing number of variants are inevitably reported. Atypical EEG abnormalities have been repeatedly found in genetic generalized epilepsies [18]. Atypical presentations and comorbidities have been reported in people with benign epilepsy with centro-temporal spikes [19]. Different epilepsy syndromes presenting with absence seizures have been identified but differences in onset age, genetic background and response to treatment, which manifests as a continuum, makes nosological classification challenging [20]. This move from the original description of an epilepsy syndrome may explain the loss of clear boundaries between, for example, focal and generalised seizures, idiopathic and symptomatic epilepsies, and even for epilepsy syndromes. Epileptic seizures are the end-product of anatomical and electrophysiological abnormalities which characterise a specific phenotype in which the individual's genetic background also plays a role. All these elements can hardly be combined in a simplified manner when taxonomy is being developed. Another limitation (relevant for health care planners and epidemiologists) is the flexibility of the instrument that may prevent a link to the preceding classifications in order to preserve continuity and monitor disease trends over time (see also below).

Are the latest classifications of seizures and epilepsies really different from the older classifications?

If we compare the present classification of the epilepsies to the 1989 classification, it easy to see that, with few exceptions, no major modifications have been introduced in the terminology [21].

The two major changes suggested in the 2010 proposal (the previous version of the present classification) [12], i.e. the elimination of the terms "*focal epilepsies*" vs. "*generalised epilepsies*" and "*idiopathic epilepsies*" vs. "*symptomatic epilepsies*", while being innovative and in line with more recent research findings, was thought to contrast with the previous terminology without introducing more clarity. For example, the dichotomy between "*focal*" and "*generalised*", which is mostly driven by seizure types, is becoming increasingly untenable, but has important implications for predictions of prognosis and the choice of effective treatment. Several reports described focal features in idiopathic generalized epilepsies [22]. Misdiagnosis of focal epilepsy as idiopathic generalized epilepsy is a possible explanation in some cases but focal features can also be an integral component of idiopathic generalized epilepsy or idiopathic generalized and focal epilepsy may coexist in the same individual. For this reason, in the present classification a new category of "*combined generalised and focal epilepsies*" has been included and cases with unconfirmed focal or generalised findings can be classified as "*unknown*". These two categories, however, replace with different terms the "*undetermined epilepsies*" of the 1989 classification. The other suggested change, i.e. the use of the term "*genetic or presumably genetic*" to replace the term "*idiopathic*", was revised as it could be interpreted as an attempt to label as "*genetic*" all cases with unknown aetiology, which was not the intention. The term "*idiopathic*" was retained in four epilepsy syndromes (Childhood Absence Epilepsy, Juvenile Absence Epilepsy, Juvenile Myoclonic Epilepsy and Generalized Tonic-Clonic Seizures Alone) for which a clear genetic aetiology could not be universally found, but the term "*genetic generalised epilepsy*" was coined to classify cases in which a clear genetic aetiology could be postulated.

The ILAE Classification as a reference for other classifications

The World Health Organization (WHO) International Classification of Diseases (ICD) has been used to classify causes of morbidity and mortality such as epilepsy for over 50 years. The ICD codes must be structured to preserve the WHO purpose of defining the overall burden of the disease in terms of frequency, cause–effect relationship, complications, mortality, and costs. The ICD codes undergo periodic revisions to be in line with the advancements of scientific knowledge. When preparing a revision of the ICD epilepsy codes, a compromise is needed between the structure of the most updated ILAE classification of epilepsy and the revised ICD codes. To assess comprehensively the overall disease burden, contrary to the ILAE purposes, WHO requires the assessment of seizures and epilepsy. The WHO also has to accept the limitations of classifying cases, due to disparities in the availability of technology and expertise in the individual countries. With this background, the WHO has been working with the advice of international experts in every

medical field, including epilepsy, on the upcoming revision of ICD-10 (i.e. ICD-11) [23-25]. The new ICD-11 codes have been aligned with the structure of the new ILAE classification, incorporating epilepsy syndromes, aetiologies and seizure-related codes, including acute symptomatic seizures, status epilepticus, and seizure complications, such as sudden unexpected death in epilepsy (SUDEP) [26]. The ICD-11 does not retain the flexibility of the ILAE classification of the epilepsies and seizures, but it reflects the aetiological perspective.
The alignment of ICD-11 with the new ILAE organisation of the epilepsies and seizures is promising, but it will be important to ensure that processes are in place to incorporate new epilepsy advances continuously in ICD-11 so that serious gaps in data collection do not occur [27].

A single multidimensional classification or different classifications for different purposes?

As suggested in 2012 [28], assuming that the new ILAE classification system calls for a multidimensional approach, the parameters in one dimension should be as independent as possible from the parameters in the other dimensions. This requires every dimension to be present and to contribute to the synthesis of all dimensions. To maintain the classification system within the limits of a pragmatic, usable instrument, however, several aspects that could be of interest to some users are, at the same time, redundant or even inapplicable for other users. In contrast, supporters of different classifications for different purposes can achieve each purpose separately but are often against linking the classifications. For example, while clinicians may be interested in an instrument which includes all the elements needed to make a correct diagnosis and predict the outcome of the disease and the response to treatment, health care providers may prefer an instrument which is easily used and that does not leave room to misinterpretation and, consequently, an incorrect coding. The expectations of researchers differ according to the scientific background and the research field. For example, epidemiological studies may not achieve diagnostic precision as investigators lack access to clinical records, as they lack the knowledge and training to make specific epilepsy diagnoses, or because there is no access to the level of specialty care needed for specific diagnosis [29]. In the absence of detailed, consistently collected classification information, an alternative is to collect more basic information elements. At a minimum, these include the age at onset, the typical manifestations (seizure types), and the underlying cause (aetiology). In contrast, geneticists, electrophysiologists, neuroradiologists, pathologists and clinical trialists may wish to expand categories reflecting their respective research fields.

The need to validate

By definition, any instrument used to classify a given disease should be proven valid and reliable. Validity is the extent to which the classification is well-founded and corresponds accurately to the real world. Reliability is the overall consistency of the results of the use of the classification. These two measures should be assessed in a field test to define the overall accuracy of the classification. In this regard, the new ILAE classification may need to be tested in the field to verify its applicability and its consistent interpretation of categories at all levels of detail. The WHO is planning a field test to verify applicability, validity and reliability of the ICD-11 codes which is a good example to follow.

Expert commentary

The new ILAE classification of epileptic seizures and epilepsies is a laudable advance in the attempt to devise a multidimensional instrument in line with present scientific knowledge. There are, however, still some aspects of the present classification which need to be clearer. First of all, depending on the extent of the diagnostic work-up, a case could be classified in different categories. For this reason, the category "*unknown*" could have different explanations according to the extent of the diagnostic ascertainment. Secondly, although flexibility is needed in clinical practice, it has negative implications for coding and research purposes. Thirdly, an algorithm including separate codes depending on the level of the diagnostic work-up has not been developed to put each case in the best available diagnostic class. Fourthly, there is no indication of the boundaries of epilepsy syndromes and to what extent syndromic variants should be included. Perhaps a clearer definition is needed for the main syndromes, which could be categorised according to different levels of diagnostic certainty depending on phenotype and genotype. Fifthly, there is no mention of the dichotomy between acute symptomatic and unprovoked seizures, two entities with different significance for the risks of seizure recurrence and of death [30]. Lastly, comorbidities are ill-defined and there is no clear indication of the role of comorbid disorders in the classification of epilepsies. Concurrent diseases with aetiological significance should be separated from clinical conditions sharing common pathogenic mechanisms with epilepsy.

We feel, as do others [28], that the purpose of a classification system should be clarified first and then a classification system should be developed that best accomplishes that purpose and which can then be used universally when classifying individuals with epilepsy. In this regard, the flexibility of the present classification in terms of permitting many parameters (seizure type, EEG patterns, gene associations, etc.) may be of little help.

Five-year view

Given the limitations of the present instruments, formal procedures should be put in place to compare the validity and reliability of the present classifications with those of the old classifications. Field tests are awaited to verify the comparative applicability and accuracy of both instruments when used in clinical practice.

An instruction manual should be prepared as an accompanying document to the classification of the epilepsies, as has been done with seizure types. Precise definitions could be provided in the manual to clarify the criteria for the diagnosis of epilepsy syndromes.

A more detailed definition should be given for aetiology, identifying the clinical conditions with an aetiological role along with the criteria used to define a cause-effect relationship. The main comorbidities should also be included along with the definition of comorbidity and the selection of clinical conditions thought to be associated with epilepsy.

Key issues

- The new ILAE classification is an attempt to reconcile the improved knowledge about epileptic seizures and epilepsies with the different requirements of stakeholders
- As compared to the old classification and its previous revisions, the new ILAE classification presents limited changes but a certain degree of flexibility
- A flexible structure represents an advantage when the classification is in the hands of different users but it is a hurdle when it’s linked to the antecedent classification schemes to understand the burden and trends of the disease with time and place
- Perhaps different classification systems should be developed for different uses and different users.

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