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Could the 2017 ILAE and the four-dimensional epilepsy classifications be merged to a new "Integrated Epilepsy Classification"?

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ABSTRACT

Over the last few decades the ILAE classifications for seizures and epilepsies (ILAE-EC) have been updated repeatedly to reflect the substantial progress that has been made in diagnosis and understanding of the etiology of epilepsies and seizures and to correct some of the shortcomings of the terminology used by the original taxonomy from the 1980s. However, these proposals have not been universally accepted or used in routine clinical practice. During the same period, a separate classification known as the "Four-dimensional epilepsy classification" (4D-EC) was developed which includes a seizure classification based exclusively on ictal symptomatology, which has been tested and adapted over the years. The extensive arguments for and against these two classification systems made in the past have mainly focused on the shortcomings of each system, presuming that they are incompatible. As a further more detailed discussion of the differences seemed relatively unproductive, we here review and assess the concordance between these two approaches that has evolved over time, to consider whether a classification incorporating the best aspects of the two approaches is feasible. To facilitate further discussion in this direction we outline a concrete proposal showing how such a compromise could be accomplished, the "Integrated Epilepsy Classification". This consists of five categories derived to different degrees from both of the classification systems: 1) a "Headline" summarizing localization and etiology for the less specialized users, 2) "Seizure type(s)", 3) "Epilepsy type" (focal, generalized or unknown allowing to add the epilepsy syndrome if available), 4) "Etiology", and 5) "Comorbidities & patient preferences".

1. Introduction

Over the last few decades there have been several proposals by various ILAE Commissions for a classification scheme for seizures and epilepsies. The ILAE classifications have been updated many times to reflect the substantial progress that has been made in diagnosis and understanding of the etiology of epilepsies and seizures and to correct some of the perceived shortcomings of the terminology used by the original taxonomy published in the 1980s [1–4] and earlier revisions from the 2000s [5]. However, these proposals have not been universally accepted, and some of them have failed to convince the community to use them in routine clinical practice [5]. During the same period, a separate classification known as the "Four-dimensional epilepsy classification" (4D-EC) was developed which includes a seizure classification based exclusively on ictal symptomatology and this system has been tested and adapted over the years [7–19]. This classification was perceived by some as being useful mainly for epilepsy surgery centers but has been thought by some to be too detailed for use by nurses, primary care physicians, and general neurologists.

The arguments for and against these two classification systems have focused on the shortcomings of each system, presuming that they are fundamentally incompatible, despite the fact that the two systems have actually been converging and now share a lot of common ground. After extensive explanations and discussions of the pros and cons of one versus the other approach in *Epilepsia* and *Epileptic Disorders* in 2019 [18–20] and debates on the two classification systems during the 12th International Epilepsy Colloquium in Lyon in May 2019 and the 33rd International Epilepsy Congress in Bangkok in June 2019, most of the differences between the systems have been highlighted and many arguments have been exchanged. An even more detailed discussion of the differences and shortcomings will be unproductive and is unlikely to convince epilepsy, general neurological or multi-professional communities to use either system.

We feel it is time, therefore, to take a closer look at the concordance between these two approaches that has evolved over time and to consider whether a unified classification incorporating the best aspects of the two approaches is feasible.

In order to facilitate discussion we outline here a concrete proposal showing how such a compromise could be accomplished by proposing an "Integrated Epilepsy Classification".

2. Assessment of similarities and common ground

A schematic representation of the two systems (Fig. 1) demonstrates that the 2017 ILAE epilepsy classification (EC) uses 5 categories (dimensions): seizure type, epilepsy type (focal, generalized, focal and generalized and unknown), epilepsy syndrome, etiology and comorbidity. By contrast, the 4D-EC distinguishes four categories (dimensions): seizure type, epileptogenic zone (providing exact localizing information or unknown), etiology and comorbidity.

The categories are listed below in order of coherence starting with those categories in which both classification systems essentially converge.

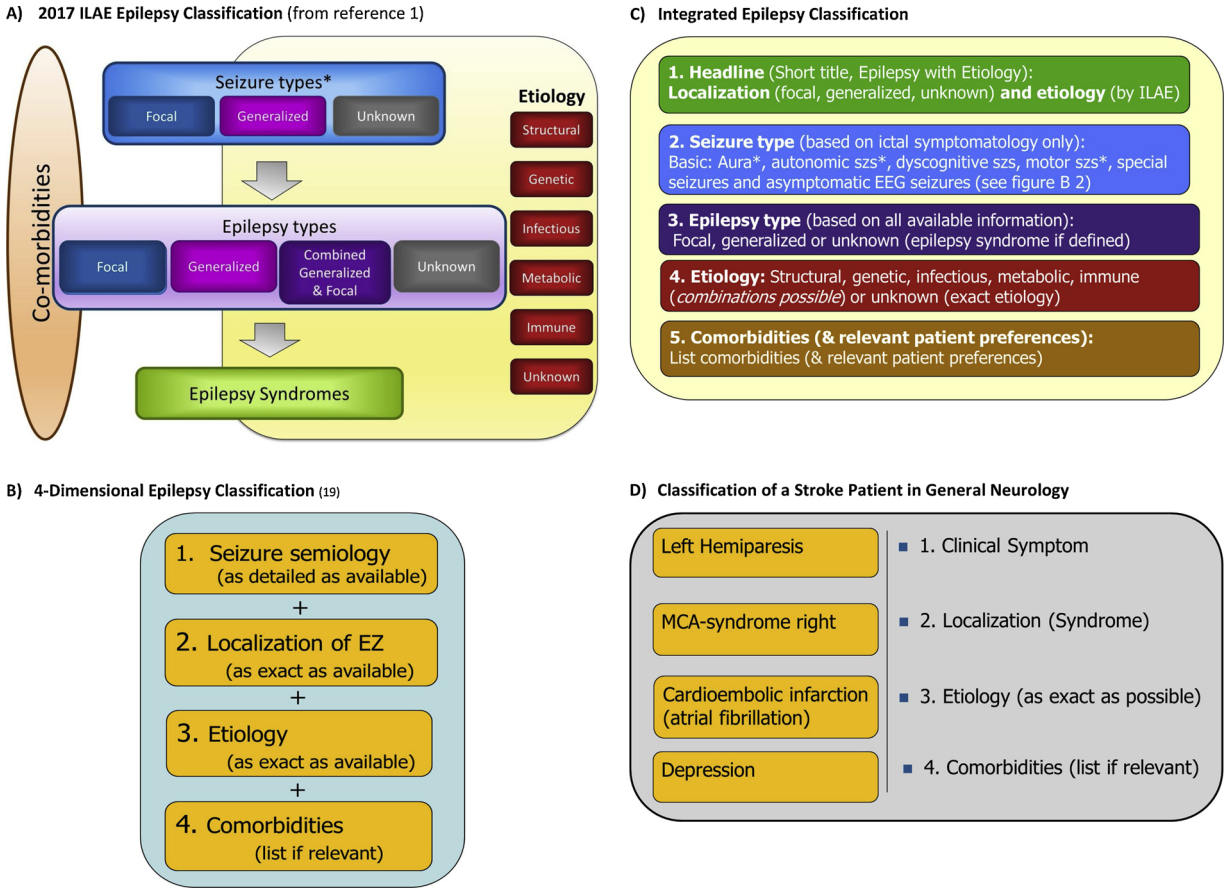


Fig. 1. This figure shows an illustration A) of the 2017 ILAE Epilepsy Classification [1], B) of the 4-Dimensional Epilepsy Classification [19], C) of the proposed Integrated Epilepsy Classification and D) an example of a classification of a stroke patient for comparison with the ECs shown above.
A) ILAE Epilepsy Classification (from reference [1]).
B) 4-Dimensional Epilepsy Classification [19].
EZ = epileptogenic zone (for definition see reference [24]).
C) Integrated Epilepsy Classification.
The (*) indicates seizure types in which a somatotopic modifier can be specified.
D) Classification of a Stroke Patient in General Neurology.
MCA = middle cerebral artery.

I **Etiology**: Both systems agree on the use of ILAE terminology (structural, genetic, infectious, metabolic, immune and unknown) and that these terms may be combined (e.g. "structural and genetic"). The main difference is that in the 4-dimensional classification the exact cause is specifically added in parenthesis. Both systems acknowledge the importance of etiology and our increasing ability to identify it. Both allow us to express that etiology may be "unknown", motivating further investigation. In the 4D-EC the exact etiology is spelled out when known (and actually listed separately), instead of simply grouped into one of the five etiology categories as posited by the ILAE-EC.

In summary, the two classification systems are well aligned here.

II **Comorbidity:** The increasing relevance of comorbidities led to their incorporation by both systems. In the 4D-EC all (relevant) comorbidities are listed as dimension 4 (in older versions this was called "related medical conditions" and patient preferences such as "further pregnancies planned" were part of the list). The ILAE-EC states that "like etiology, it is important that the presence of comorbidities be considered for every patient with epilepsy at each stage of classification, enabling early identification, diagnosis, and appropriate management" without defining where and how exactly to include this information into the classification.

Again, it can be seen that there is very high agreement between the 2 EC systems.

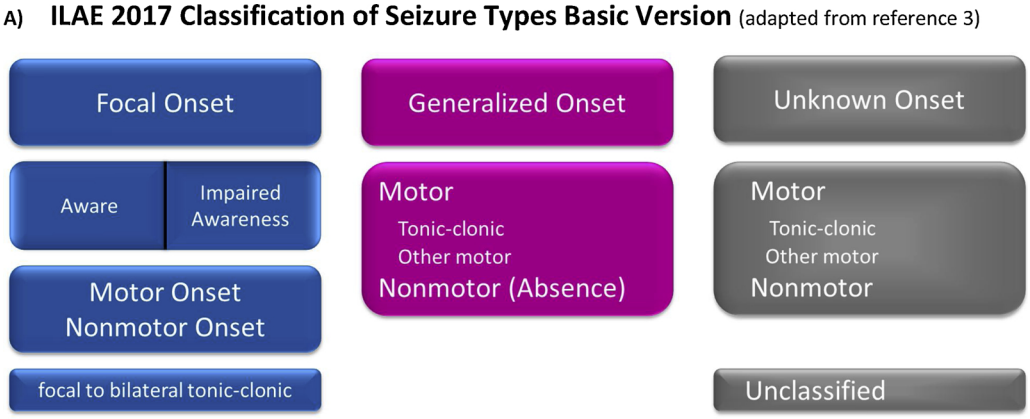
III **Epilepsy type**: In the ILAE-EC information from different sources (history including seizure symptomatology, clinical examination, imaging, EEG, and laboratory results, including genetic testing) is used to allow classification by localization of seizure type (focal, generalized, combined generalized and focal, or unknown). In the 4D-EC, the corresponding dimension 2 is called "epileptogenic zone (EZ)" and the same data are used by the ILAE to localize the EZ as precisely as possible (e.g. unknown, generalized, left precentral hand area (and therefore by definition focal), etc.). The requirement to localize the EZ as precisely as possible with the available information has led to the critique that the 4D-EC was geared toward a surgical approach (where such detail is essential) and was not useful for the general medical community or for research where more broad categories are required [6]. However, a compromise is readily available using focal, generalized or unknown as the main category and then encouraging the classifier to list the location of the epileptogenic zone with as much precision as possible depending on the expertise of the classifier and the available information.

IV **Epilepsy syndrome**: Both systems allow specification of an epilepsy syndrome (Juvenile Myoclonic Epilepsy, Dravet Syndrome, GEFS+, GluT1-deficiency, etc.) because they convey valuable "gestalt" information, which helped to identify the genetic etiology of some of the syndromes mentioned. Furthermore, in some cases different mutations (i.e. loss or gain of function mutations) to the same gene

may result in different syndromes, e.g. Dravet vs GEFS +. The current ILAE-EC considers epilepsy syndrome to be indispensable, while the proponents of the 4D-EC argue that the identification of epileptic syndromes will likely become less relevant over the coming decades as management relies increasingly more and more on precise molecular diagnosis of etiology. Of note, however, even if the 4D-EC deemphasizes the importance of epileptic syndromes, it does allow epilepsy syndromes to be listed in parenthesis after specifying the epileptogenic zone.

Also in this category there is good agreement and a compromise is easy to find.

V **Seizure type:** Both classification systems are based mainly (ILAE-EC) or exclusively (4D-EC) on ictal symptomatology and allow different levels of detail. Both allow use or omission of "awareness" as a classifier [4,19]. However, there are significant discrepancies between the two EC systems in this dimension. The ILAE seizure type classification (based mainly on the 1981 seizure classification), like the ILAE epilepsy type classification includes all available information from different sources (history, including seizure symptomatology, clinical examination, imaging, EEG and laboratory results, including genetic testing), and also etiology and comorbidities (see above). Therefore, in the ILAE-EC the seizure type usually determines the epilepsy type, and the two dimensions are not independent. Accordingly, terminology and color codes used for seizure type and epilepsy type are nearly identical (Fig. 1). In order to classify a seizure in the ILAE-EC, 12 rules apply [4]. Initially, it has to be decided if seizure onset is focal, generalized, or unknown (< 80 % confidence). Only if the onset is focal, the preservation or loss of awareness is specified. According to rule 3, all seizures with any impairment of consciousness during the course of the seizure are classified as "focal impaired awareness seizures (FIAS)", a term that corresponds to the old term "complex partial seizure". According to rule 2, however, one can also decide to omit awareness as a classifier [4]. The basic version contains 11 seizure types (Fig. 2a). The extended version of the seizure classification contains a relatively restricted list of seizure types that is different for each the focal, generalized or unknown onset category of seizures [3]. Therefore, for example, seizures of generalized or unknown onset with prominent automatisms, known to be relatively frequent [21] and part of older classifications [22], are not included in the 2017 ILAE-EC. However, an extensive glossary is provided, that encourages detailed additional description of seizures which then does allow to include some localizing information [4]. As a result, the process of seizure classification is actually quite complex, and the likelihood that two different investigators will classify the same seizure identically seems low, unless only basic terminology is used. The ILAE-seizure classification (ILAE-SC) does not include a formal description of seizure evolution, except for the "focal to bilateral tonic-clonic" seizure type, so that information on symptomatology during seizures might be overlooked.



a somatotopic modifier can be specified.

Fig. 2. The most basic version of A) the ILAE-EC seizure classification [3,4] and of B) the 4D-EC seizures classification [19]. As shown, the basic version of the ILAE-SC defines 11 seizures types, namely, 1) focal aware motor onset seizures, 2) focal aware nonmotor onset seizure, 3) focal impaired awareness motor onset seizure, 4) focal impaired awareness nonmotor onset seizure, 5) generalized onset tonic-clonic seizure, 6) generalized onset other motor seizure, 7) generalized onset nonmotor (absence) seizure, 8) unknown onset tonic-clonic seizures, 9) unknown onset other motor seizure, 10) unknown onset nonmotor seizure and 11) unclassified seizure. Of note, classifications with higher complexity are available for both systems. The ILAE-SC uses 12 rules and an extensive glossary of terms to be used for additional seizure description [4]. The results of different tests are included, and etiology and comorbidity should be considered when classifying the seizure type. The 4D-EC seizures classification depends exclusively on ictal symptomatology (semiology). Somatotopic modifiers (*) and lateralizing signs can be added for certain seizure types or evolutions. Seizure evolutions can be depicted by listing seizure types linked by an arrow (19, see examples in the text).

A) ILAE 2017 Classification of Seizure Types Basic Version (adapted from reference [3]).

B) 4D-EC Classification of Seizure Types, Basic Version (adapted from reference [19]).

The (*) indicates seizure types in which

The 4D-EC includes the seizure classification as its Dimension 1. As mentioned above, seizure type is based exclusively on seizure semiology as given by description of the patient or an eyewitness or video-analysis. Smart phones with video-function are widely available world-wide today, so both these sources for seizure classification are available even in low-resource countries, and transmission of the data to an expert is usually possible if needed. Recent evidence shows that expert interpretation of such videos has high sensitivity (89 %) and specificity (93 %) for an epilepsy diagnosis using video-EEG as gold standard and is of value in diagnosing PNES [23]. The 4D seizure classification is hierarchical and expandable as needed. In its basic version it is comprised of 6 distinct classes: Auras, autonomic seizures, dyscognitive seizures, motor seizures, special seizures and asymptomatic EEG seizures (Fig. 2b). When classifying a given seizure, successive semiological components are listed in order, separated by arrows to indicate - at least theoretically - sequential propagation of the ictal discharge through distinct brain regions. Additional details of semiology (aura, dyscognitive symptoms, description/somatotopic location of motor manifestations, etc.) are also listed since they have potential implications for EZ localization. The effort to define phenomenology as accurately as possible using non-overlapping subclasses that are organized in a clear hierarchical order is similar to the clinical approach used to classify any neurological symptom or deficit (Fig. 1D). A major difference between the ILAE-EC and 4D-EC is the relative emphasis on awareness and auras. Awareness is fundamental to the ILAE-EC categorization of focal seizures but not formally included as a major classifier in the 4D-EC. In the 4D-EC, the nature of awareness change is described in detail and the expression "(LOA)" (loss of awareness) added in the sequence to the first seizure component during which altered consciousness is observed. Besides, aura symptoms are considered to be critically important by the 4D-EC based on the idea that they provide highly specific information about seizure origin and therefore are explicitly detailed, whereas the ILAE-EC classifies auras more generally as part of the focal aware seizure (FAS) class. A major advantage of the 4D-EC seizure classification is that it is conceptually straightforward: while a very high level of detail can be included if needed and available, at its basic level the 4D-EC outlines information about seizure initiation and progression, and the value of this information is not restricted to epilepsy surgery centers [19]. In clinical practice, there is a lack of an accurate seizure description for most patients (who would not have monitoring). A classification scheme allowing detailed semiological seizure classification including seizure evolution would provide an anatomico-functional perspective and help to differentiate not only focal from generalized onset seizures but also to differentiate epileptic seizures from other non-epileptic events . [24].

In summary, there is only partial agreement between the two EC, making a compromise on this category considerably more challenging than the others.

VI **Epilepsy with etiology.** The 2016 ILAE-EC proposal for discussion contained a 6th category named epilepsy with etiology [2]. The argument has been made repeatedly that both classification systems are too complex for the use by nurses, nurse practitioners, primary care physicians, general neurologists, and other stakeholders. This category was suggested to bring together the basic data on epilepsy type (localization) and etiology (6 categories mentioned above). This will serve to provide essential information for the less specialized individuals in the team and promote rapid, efficient communication. Therefore, reintroduction of this category would be helpful (see "Headline" below).

3. Proposal for an integrated epilepsy classification with headline

Based on the assessment of similarities and conversions we propose a fused ILAE/4D classification that incorporates the best of the ILAE-EC and 4D-EC. We aim for a simple and easy to use classification addressing the needs of the epilepsy community at large including specialized epileptologists in the clinic, epilepsy researchers, neurosurgeons, and those with a more general practice.

1 **Headline/Epilepsy Core: Localization** (Focal, generalized or unknown) **Etiology** (category, combinations possible). (Source: ILAE-EC)
2 **Seizure type(s):** Semiological seizure classification, allowing for description of seizure evolution (arrows). Add (LOA) if awareness is impaired. (Source: 4D-EC > ILAE-EC)
3 **Epilepsy type:** Focal, generalized or unknown. If an epilepsy is focal, provide location of the epileptogenic zone as exact as possible or needed, and add epilepsy syndrome in parenthesis if available (such as benign focal epilepsy of childhood); if generalized, provide epilepsy syndrome in parenthesis if available; if unknown add nothing. (Source: ILAE-EC = 4D-EC)
4 **Etiology:** Use ILAE class or combination thereof (e.g. genetic and metabolic) and add exact etiology (e.g. focal cortical dysplasia type 2B) in parenthesis if available. (Source: ILAE-EC = 4D-EC)
5 **Comorbidities (& relevant patient preferences):** List all relevant comorbidities and add patient preferences if important for management (e.g. plans to start a family soon, febrile seizure at age 8 month, etc…). (Source: ILAE-EC = 4D-EC)

4. Illustrative examples

A)

1 **Headline: Focal structural and genetic epilepsy**
2 **Seizure type:** Left visual aura - > left versive (LOA) - > bilateral tonic-clonic seizure
3 **Epilepsy type:** Focal (right mesio parieto-occipital)
4 **Etiology:** Structural and genetic (focal cortical dysplasia type 2B)
5 **Comorbidities, relevant patient preferences:** Depression, carbamazepine allergy, plans to have more children

B)

1 **Headline: Generalized genetic and metabolic epilepsy**
2 **Seizure types:** 2.1 Hypomotor seizure, 2.2. Bilateral symmetric tonic seizure, 2.3 subclinical EEG-seizure
3 **Epilepsy type:** Generalized
4 **Etiology:** Genetic and metabolic (GluT1 deficiency)
5 **Comorbidities:** Cognitive and motor developmental impairment

5. Explanation and discussion by category

1 **The Headline** (Epilepsy Core or Summary Line) represents a short summary of the essential information about epilepsy type and etiology which are most relevant for the management of a patient and could be the common core information for rapid and effective inter-professional communication. This is the minimum information that should be available and used by everybody involved in a patient´s management. As mentioned above, this category is based on the ILAE suggestion of "epilepsy with etiology" [2]
Examples:
a) Focal epilepsy unknown etiology
b) Focal structural & genetic epilepsy
c) Generalized genetic epilepsy
d) Generalized genetic and metabolic epilepsy
2 **Seizure type(s):** We suggest the use of an exclusively semiological seizure classification as suggested by the 4D-EC for several reasons. First, it is based on information that is objectively observable and universally available (using patient/eyewitness report and video). Second, it is scalable, being very easy to use in the basic version

(only 6 seizure types) but expandable to allow specification of as much detail as available and needed, including evolution, body side and parts involved, lateralizing signs, and loss of awareness (if present) during a seizure. Third, it provides clearly defined distinct non-overlapping terminology in hierarchical order, preventing different seizure descriptions by different investigators [19] and no free text. Finally, ictal semiology reflects our general knowledge on the functional anatomy of the human brain and is a great teaching tool [24]. The exact terms to be used (e.g. hyperkinetic vs. hypermotor or dyscognitive vs. cognitive) are less important and can be discussed and defined later.

Examples:

a) "Motor seizure (LOA)". Definition: Seizure with prominent movements as the main seizure manifestation. During the seizure the patient was unresponsive and he was amnestic after the seizure. No further reliable information is available.
b) "Bilateral myoclonic - > bilateral tonic-clonic seizure (LOA)". Definition: Typical myoclonic tonic-clonic seizure in a patient with JME. The patient was aware during the bilateral myoclonic seizure.
c) "Left visual aura - > left versive (LOA) - > bilateral tonic-clonic seizure".
d) "Epigastric aura - > automotor seizure. Lateralizing sign: automatism with retained awareness". Explanation: This evolution has been shown to be associated with a non-dominant [25] temporal lobe epilepsy in > 95 % of patients [26] and shows that this seizure classification results in relevant clinical information. Previously it had been postulated that all focal seizures with automatisms were associated with LOA.

3 **Epilepsy type:** The question about whether an epilepsy is focal or generalized/unknown is of major importance for choosing the appropriate antiseizure drug (ASD) and to determine if epilepsy surgery is a treatment option. The determination of whether or not it is focal depends on the localization of the epileptogenic zone and seizure onset zone rather than on the seizure semiology [27]. This category includes information from all available tests (including seizure semiology, history, clinical examination, neuroimaging, EEG, lab results, etc...) that help localize these zones and define the epilepsy type. Therefore, while using the ILAE-EC term "epilepsy type" rather than "epileptogenic zone", the definition of the epileptogenic zone is still of major importance and closely related. We suggest first to defining if the epilepsy type is focal, generalized or unknown. The localization of the epileptogenic zone should then be stated as exactly as possible and/or needed if dealing with a focal epilepsy. The epilepsy syndrome, if available/needed, should then be added in parenthesis. If the epilepsy type is generalized the epilepsy syndrome - if any - should then be added in parenthesis. Nothing will be added if the epileptogenic zone is unknown. Patients with a focal and generalized epilepsy would have two separate conditions. An example would be a patient with a generalized genetic epilepsy (GEFS +) and a focal structural epilepsy (right mesial temporal lobe epilepsy).

Examples:

a) Focal epilepsy
b) Focal left mesiotemporal lobe epilepsy
c) Focal right fronto-temporal epilepsy (Benign focal epilepsy of childhood)
d) Generalized epilepsy (Juvenile myoclonic epilepsy/Janz-Syndrome)

4 **Etiology:** The etiology is classified as suggested by the ILAE-EC into either structural, genetic, infectious, metabolic, immune, a combination of these or unknown. If known the exact etiology may be added in parenthesis.

Examples:

a) Genetic (SCN1A LOF mutation)
b) Structural and genetic (bilateral periventricular heterotopia; Filamin A mutation)
c) Structural (Glioblastoma)
d) Genetic and metabolic (GluT1 deficiency, SLC2A1 mutation)

5 **Comorbidity (& patient preferences):** Both classification systems stress the importance of comorbidities. We suggest listing all relevant comorbidities as well as other management relevant factors including patient preferences and risk factors/outcome predictors such as a history of febrile seizures confirmed by a caretaker of the patient.

Examples:

a) Depression
b) History of febrile seizure at age 8 month
c) Carbamazepine allergy
d) Left temporal lobe resection (2000)

6. Summary

In summary, based on a significant amount of common ground of the ILAE-EC and the 4D-EC, we propose to merge the classifications in order to include essential features of each system. It includes a headline, seizure type, epilepsy type and syndromes, etiology and comorbidities. Based on this simple structure as much detail as available can easily be added if required. The introduction of a headline (epilepsy with etiology) should facilitate its broader use, including for inter-professional communication. This "Integrated Epilepsy Classification" will help serve as the basis for a productive discussion that no longer focuses on the differences, but on the similarities and advantages of both systems, incorporating progress made in diagnosing epilepsy since the 1980s. Following or simultaneous to such intensive open discussion of our proposal it appears desirable to compare the usability and utility of the classification systems prospectively in a large number of patients of different ages and in different settings, including in normal resource and resource poor countries.

Declaration of Competing Interest

The authors have no conflicts of interest with respect to this manuscript.

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