Title: New ILAE versus previous clinical status epilepticus semiologic classification: Analysis of a hospital-based cohort.

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Journal: Epilepsia

Year: 2016 Jul

Issue: 57

Volume: 7

Pages: 1036-41

DOI: 10.1111/epi.13403

New ILAE versus previous clinical Status epilepticus semiological classification: analysis of a hospital-based cohort

Running title: new vs old ILAE SE classification

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Contents:

Title (characters): 118 (running title: 34 characters)

Abstract (words): 245

Main text (words): 2308

Figures: 2

Tables: 3

References: 29

Keywords: Clinical features, outcome, prognosis, seizure, epidemiology.

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Abstract

Objectives

In 2015, the ILAE has issued a new Status epilepticus (SE) classification, including a detailed semiological axis. This study assesses frequencies of SE forms in a cohort of adult patients, and explores differences and practical implications as compared to a seizure-type-bound classification.

Methods

The prospective adult SE registry of the CHUV was considered over 5 years (2011-2015); each SE episodes was retrospectively reclassified for its semiology according to the new ILAE scheme. Mortality rates were retrieved for each subgroup of SE.

Results

Among 488 SE episodes, according to the seizure-type-bound classification, 230 (47%) had a generalized convulsive, and 29 (6%) a nonconvulsive SE in coma; both categories overlapped almost perfectly between the two classifications. However, the 84 episodes with focal SE without consciousness impairment and the 141 episodes with consciousness impairment were each translated into 2 major (and 5 sub-) categories of the new ILAE classification, having markedly different mortality rates. Also, of 140 episodes labeled as focal motor SE according to the new classification, 54% had concomitant consciousness impairment, while 46% not; again, mortality rates were heterogeneous.

Significance

While generalized convulsive and nonconvulsive SE in coma show an almost perfect correspondence across SE semiological classifications, focal SE is markedly heterogeneous and appears to be better reflected in the new classification, offering more clinically relevant subdivisions, also differing in mortality rates. This refined knowledge may allow designing more precise clinical prognostic scores than existing tools, and should be taken into account for epidemiological studies.

Key points

- Focal SE, regardless of related consciousness impairment, represents a markedly heterogenous condition, also in terms of mortality rate.
- Future epidemiological studies should report both classifications to allow comparisons with previous findings.

- The new ILAE SE classification should include a modifier for consciousness impairment for the item “A.3. Focal motor”.

Introduction

Status epilepticus (SE) represents one of the most frequent neurological emergencies with potentially fatal outcome [1, 2]; over the last decade, increasing attention has been devoted to its clinical management [3-6] and outcome prediction [7, 8]. Seizure type or semiology during a given SE episode represents not only a prognostic predictor [7], but may also be used to orient the treatment flow.

The current therapeutic guidelines in Europe [5] and North America [4] use a relatively simple classification derived from the ILAE seizure classifications of 25-35 years ago [9, 10], mainly dichotomizing SE into convulsive and nonconvulsive (including absence, focal with impaired consciousness or complex partial [11], and subtle [12] or nonconvulsive SE in coma). Of note, this type of classification was not developed, nor was it endorsed by the ILAE. In fact, in the ILAE classification SE was relegated to the addendum [10], where it was defined as a "seizure that persist for a sufficient length of time, or is repeated frequently enough that recovery between attacks does not occur". It was subdivided to partial (i.e. Jacksonian) or generalized, and when "very focal" referred to "epilepsia partialis continua". In 2001, the ILAE glossary of terms [13] defined SE as "a seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures of that type in most patients or recurrent seizures without interictal resumption of baseline central nervous system function". The Core Group of the Commission on Classification and Terminology of the ILAE included SE in a list of seizure types, which was far from complete [14]. Neither the SE classification of 1981, nor its modifications from 2001 and 2006 were widely accepted and used by the clinical community, which instead developed a dichotomized classification (convulsive vs. non convulsive SE), as described above [4, 5, 15]. However, the ILAE recognized the fact that SE cannot be adequately described according to "seizures" alone, and therefore a new SE definition and classification has recently been proposed by the Task force on Classification of Status Epilepticus [16]. In the new classification, seizure semiology is the first of four axes (completed by etiology, EEG features, and age), and represents the cardinal feature of this approach. While the primary dichotomy is between

prominent motor symptoms and nonconvulsive forms, the taxonomy also includes the level of impairment of consciousness (comatose vs. non comatose).

Given that to the best of our knowledge no practical assessment has been conducted using the new ILAE classification, is still unclear how this compares with previous classifications used for example in current therapeutic guidelines. The aim of this study was to assess the frequencies of SE forms in a large cohort of adult patients, and to explore differences and practical implications of these two clinical classifications.

Methods

We analyzed the SE registry of the Lausanne University Hospital (CHUV), which is approved by the Institutional review board (given its purely observational character, patients' consent are not needed) for the period between January 2011 and December 2015. Convulsive (tonic-clonic) SE was defined as the occurrence of continuous or repetitive seizures without complete recovery of baseline clinical conditions for ≥5 min [17]. The registry has been described in detail previously [18, 19]; for each SE episode managed in the CHUV in patients over 16 years, excluding postanoxic etiologies, demographical and clinical items are entered prospectively since 2006 by physicians of the EEG/epilepsy unit (supervised by AOR and JN) and a study nurse working on the project since 2010 (CS); this assures a high internal validity and coherence over the years. In particular, the worst seizure type at each episode onset (i.e.: up to treatment start) was prospectively assessed according to direct observation or the reports of consulting physicians and emergency teams, and classified into the following order of increasing severity (according to [10] : absence, focal without consciousness impairment or simple-partial, myoclonic in genetic generalized epilepsy; focal with consciousness impairment or complex-partial; generalized convulsive; nonconvulsive in coma (including subtle myoclonic movements), as seen in **Table 1**, left column. In November-December 2015, CS and AOR reclassified with the help of patients' charts each episode until 2011 according to the newer ILAE guidelines, as shown in **Table 2**, left column [16]; discrepancies were resolved by discussion. Etiologies were considered as potentially fatal, as previously described [18, 19], if leading to death without a specific treatment. The

validated Status Epilepticus Severity Score (STESS) was calculated upon admission and used to stratify episodes according to their gravity. [20, 21]

Frequencies of SE episodes and the relative mortality rates were described according to the two classifications. Furthermore, in order to explore in more detail the potential heterogeneity resulting from the comparisons, episodes previously classified as "Focal with consciousness impairment" were further detailed in the newer taxonomy, as were episode newly labeled as "A.3 Focal motor" towards the previous clinical classification (i.e., including information about consciousness impairment). Differences in important SE outcome predictors (such as age, occurrence of potentially fatal etiologies and STESS) between focal with- and without consciousness impairment (among repetitive focal seizures) were explored using the t-test, χ^2, or the Mann-Whitney-U-test, as needed.

Results

Over the five considered years, 488 consecutive SE episodes (230 women; median age 66 years, range 16 – 93) occurring in 417 patients were retrieved; there were 64 deaths, accounting for a mortality rate of 15.3%. Thirty-one episodes (6%) lasted <30 minutes, only 4 of them labeled as focal SE with impaired consciousness (and none of absence SE).

Table 1 shows the frequencies according to the previous clinical classification; while absence SE resulted extremely infrequent, and myoclonic SE was not observed, generalized convulsive SE represented almost half of the episodes, focal SE with consciousness impairment (complex-partial) accounted for slightly more than 1/4, and focal without consciousness impairment just over 1/6; finally, nonconvulsive SE in coma occurred in 6%. Mortality was highest in the latter group, followed by focal with, focal without consciousness impairment, and generalized convulsive forms.

Table 2 illustrates the breakdown of semiological features according to the newer ILAE classification. Convulsive SE as a group (A.1) perfectly reflected generalized convulsive SE in the traditional classification and was also the most prevalent form, followed by focal motor SE

(A.3), which accounted for almost 30% of episodes. Nonconvulsive SE without coma (B.2) occurred in 1/6 of episodes. Finally, nonconvulsive SE with coma (B.1) almost completely overlapped with the synonymous form in the older classification; just one patient was scored as myoclonic SE in coma. Of note, there were no episodes of tonic, hyperkinetic and nonconvulsive SE of autonomic expression without coma.

From the viewpoint of the previous clinical classification, focal SE was translated into several categories of the new taxonomy. As illustrated in **Figure 1A,** for focal SE without impaired consciousness, repeated focal motor seizures (A.3.a) accounted for 60%, followed by nonconvulsive SE without coma, aphasic SE (B.2.b.b., 17%) and epilepsia partialis continua (A.3.b, 14%). The latter, as opposed to the two previous categories, was not associated with any mortality. For focal SE with consciousness impairment, as seen in **Figure 1b**, the two most frequent translations were into repeated focal motor seizures (A.3.a), and nonconvulsive SE without coma but impaired consciousness (B2.b.c); this again was mirrored by relevant mortality rate differences. Also, focal motor SE in the new ILAE classification and its subgroups corresponded to both focal with or without consciousness impairment (complex partial, respectively simple partial) SE in an almost balanced way (**Table 3**), showing again important differences in related case-fatality rates. These were explored looking at differences of important SE outcome predictors: among repetitive focal motor seizures, patients having focal SE with consciousness impairment were significantly older ($p=0.026$, t-test), had a nonsignificant higher STESS ($p=0.086$, Mann-Whitney), and a comparable frequency of potentially fatal etiologies ($p=0.847$, χ^2) as compared to patients with focal SE without consciousness impairment.

Discussion

This study shows that some features, such as focal SE with (complex-partial) or without consciousness impairment (simple-partial) of the previous clinical classification, and focal motor SE of the new ILAE classification, are markedly heterogeneous and can hardly be directly

translated into each other. Conversely, (generalized) convulsive SE and nonconvulsive SE in coma almost perfectly overlap.

The present hospital-based cohort, collected over a five-year period, represents a large sample of SE episodes in adults, not restricted to intensive care units. Under-ascertainment seems extremely unlikely, given that at the CHUV every adult patient with SE has an EEG, and that recruitment was conducted by the EEG/epilepsy unit; furthermore, the internal validity of the cohort is strengthened by the work of a restricted team of clinical researchers over the years. As a comparison, population-based studies show markedly divergent numbers, with mortality rates oscillating between 7% and 26%, and generalized convulsive SE occurring between 33% and 74%, with only about 1% of nonconvulsive SE in coma [22-25]. More recent hospital-based series also show a heterogeneous situation: generalized convulsive SE was observed between 22% and 60%, and nonconvulsive SE in coma between 4% and 29%; mortality rates were estimated between 10% and 24% [26-29]. These discrepancies are probably due not only to different definitions and assessments as it may be postulated for SE semiology, but also to population-specific factors, as it emerges from the short-term case-fatality rates (a non-debatable outcome): indeed, as an example, studies focusing on ICU populations or carried out in Virginia tended to have a higher mortality, while those including children showed reduced risks.

While the lack of myoclonic and tonic SE probably reflects the present cohort characteristics, without a relevant prevalence of patients with marked mental retardation and teenagers with juvenile myoclonic epilepsy, the lack of hypermotor SE is probably due to the striking rarity of this semiology. Some of these forms may also be “masked” by other more severe seizures, the episodes being eventually classified according the worst seizure type.

In the present cohort, focal SE with impairment of consciousness showed a higher mortality rate than generalized-convulsive SE. This somewhat unexpected finding may be explained by the marked heterogeneity of the former condition. Indeed, mortality rates in focal SE without (simple-partial) and with consciousness impairment (complex-partial) were clearly inhomogeneous across the corresponding new ILAE classification subgroups: 10-26% for

aphasic SE and repeated focal motor seizures, 12 % for focal dyscognitive SE, and <10% for other forms, such as epilepsia partialis continua, ictal paresis, adversive SE, and aura continua (B.2.b.a). These differences may reflect divergent biological substrates (see below), and in our view, this clearly highlights both the major heterogeneity of the term “nonconvulsive SE”, which in some assessments [24] may even include SE in coma (a condition with the highest risk of mortality), and the usefulness of the new, more detailed SE semiological classification. Similar thoughts, however, also apply to the newer category of focal motor SE, where the heterogeneity is even found within given subcategories: repeated focal motor seizures and ictal paresis unfortunately lack a subcategory informing upon consciousness impairment. In fact, patients with repeated focal motor seizures and focal SE with consciousness impairment had a clearly higher mortality as compared to those without consciousness impairment, which correlated with older age and (to a lesser extent) higher STESS, two robust SE mortality predictors.

Currently, few prognostic scores have been validated in SE, the most widely used being probably the STESS, a validated scale including an item on semiology [20, 21, 26]. As the present study shows, however, a uniform translation into the new classification is challenging, and the heterogeneity might account for some of the imprecision of this score, especially regarding focal SE. More recently, the EMSE score was proposed, which does not take into account seizure types [27]; this might represent an advantage for assessing patients studied according to different SE classifications; however, the EMSE might prove more difficult to obtain on a clinical basis within a short time. It is to hope that a refined use of the new ILAE classification, taking into account the aforementioned issues, may contribute designing more precise prognostic tools.

This study has some limitations. Being a single-center cohort, its generalizability is not straightforward. However, as detailed above, clinical SE features, including mortality, lie within the vast majority of recently published data from the Western world, and, more importantly, it reflects a very large, non-selected adult population. While the prospective assessment of SE semiology supports the quality of data ascertainment, the retrospective reclassification

according to the new ILAE recommendations may have introduced some errors. This was conducted within a short time frame by 2 (CS, AOR) authors, using the same criteria: while we cannot exclude a systematic error, it is highly unlikely that a non-systematic bias was at play. While the registry uses a uniform SE definition threshold at 5 minutes, the ILAE classification suggests 10-15 minutes for complex-partial and absence SE; since SE lasting <30 minutes occurred in only 4/145 of SE episodes of these both types, this likely did not result in a marked bias. Finally, we labeled seizures as the "worst" type at onset of a given episode. While this approach has been repeatedly used [7, 19, 29], it admittedly represents a simplification of the natural history: it has been recently shown that generalized convulsive seizures evolving towards complex-partial at the time of treatment initiation behave clinically rather like episodes starting as complex-partial SE [18]. A more sequential classification accounting for semiological changes over time may better reflect these aspects, but seems rather unpractical in a clinical registry and for the purpose of epidemiological studies.

The described frequency of SE types should be confirmed in a prospective cohort. In any case, however, an adaptation of prognostic scores including semiology will be needed. Moreover, while future epidemiological studies on SE should definitely use the new ILAE classification, it seems highly reasonable to also maintain the old labels, at least for nonconvulsive SE with or without consciousness impairment, in order to allow comparisons with previous data. Finally, it is advisable to include a modifier of "consciousness impairment" into item A.3 "Focal motor SE".

Disclosure of Conflict of Interest

Dr Rossetti and Prof. Trinka served in the ILAE task force that generated the new SE classification. The other authors do not have any conflict of interest in relationship with this study.

Required statement

Our work described here is consistent with the Journal's guidelines for ethical publication.

Table 1, semiology of each Status epilepticus episode according to the previous clinical classification.

SE Type	**Frequency** (column percentage)	**Mortality related to episodes** (row percentage)
Absence	4 (0.8%)	0 (0%)
Focal without consciousness impairment	84 (17.2%)	7 (8.3%)
Myoclonic (in idiopathic generalized epilepsy)	0	0
Focal with consciousness impairment	141 (28.9%)	28 (19.9%)
Generalized convulsive	230 (47.1%)	17 (7.4%)
Non-convulsive SE in coma	29 (5.9%)	12 (41.4%)
Total	**488**	**64**

Table 2, semiology of each Status epilepticus episode according to the ILAE classification [16].

SE Type	**Frequency** (column percentage)		**Mortality related to episodes** (row percentage)	
	New classif.	**Old classif.**	**New classif.**	**Old classif.**
With prominent motor signs				
A.1 Convulsive SE				
A.1.a Generalized convulsive	134 (27.5%)	230 (47.1%) Generalised convulsive	8 (5.9%)	17 (7.4%) Generalised convulsive
A.1.b Focal evolving into bilateral convulsive	75 (15.4%)		4 (5.3%)	
A.1.c Convulsive unknown if initially focal or generalized	21 (4.3%)		5 (23.8%)	
A.2. Myoclonic SE				
A.2.a Myoclonic with coma	1 (0.2%)	1 (0.2%) Myoclonic	0 (0%)	0 (0%) Myoclonic
A.2.b Myoclonic without coma	0		0	
A.3 Focal motor SE				
A.3.a Repeated focal motor seizures	124 (25.4%)	142 (29.1%) Simple/complex Partial	24 (19.4%)	24 (16.9%) Simple/complex Partial
A.3.b Epilepsia partialis continua	12 (2.5%)		0 (0%)	
A.3.c Adversive	2 (0.4%)		0 (0%)	
A.3.d Oculoclonic	0		0	
A.3.e Ictal paresis	4 (0.8%)		0 (0%)	
A.4 Tonic SE	0	0	0	0
A.5 Hyperkinetic SE	0	0	0	0
Without prominent motor signs				
B.1 Nonconvulsive SE with coma	28 (5.7%)	28 (5.7%)	12 (42.9%)	12 (42.9%)
B2 Nonconvulsive SE without coma				
B.2.a Nonconvulsive SE without coma, generalized	4 (0.8%)	4 (0.8%)	0 (0%)	0 (0%)
B.2.b.a Nonconvulsive SE without coma, focal without consciousness impairment	4 (0.8%)	83 (17.0%) Simple/complex Partial	0 (0%)	11 (13.3%) Simple/complex Partial
B.2.b.b Nonconvulsive SE without coma, aphasic	28 (5.7%)		5 (17.9%)	
B.2.b.c Nonconvulsive SE without coma, focal with consciousness impairment	51 (10.5%)		6 (11.8%)	
B.2.c Nonconvulsive SE without coma, autonomic	0	0	0	0
Total	**488**	**488**	**64**	**64**

Table 3, distribution of focal motor Status epilepticus and its sub- items of the ILAE classification, according to the previous clinical classification.

SE Type	**Frequency**	**Mortality**	**Frequency** (row percentage)	**Mortality** (line percentage**)**	**Age** mean (±SD)	**Potentially fatal etiology**	**STESS** median (range)
A.3.a Repeated focal motor seizures	124	24 (19.4%)	73 CP (58.9%)	19 (26.0%)	67.3 (±16.0)	46 (63%)	2 (0-5)
			51 SP (41.1%)	5 (9.8%)	60.6 (±17.3)	33 (65%)	2 (0-4)
A.3.b Epilepsia partialis continua	12	0 (0%)	12 SP (100%)	0 (0%)	44.2 (±14.1)	1 (8%)	0 (0-2)
A.3.c Adversive	2	0 (0%)	2 CP (100%)	0 (0%)	57.0	2 (100%)	2.5 (1-4)
A.3.d Oculoclonic	0	NA	NA	NA	NA	NA	NA
A.3.e Ictal paresis	4	0 (0%)	1 CP (25%)	0 (0%)	68.0	0 0%)	2
			3 SP (75%)	0 (0%)	48.0 (±21.5)	0 (0%)	0 (0-0)

CP = complex partial (focal with consciousness impairment); SP = simple partial (focal without consciousness impairment). STESSS= Status Epilepticus Severity Score.

Figure 1:

a: distribution of the categories according to the new classification corresponding to focal SE without consciousness impairment (simple partial) in the old classification. Mortality rate was 8.3% in simple partial SE according the old classification and 14.2% for nonconvulsive w/o coma, aphasic status (B.2.b.b), 10% for repeated focal motor seizures (A.3.a), and 0% for all other categories epilepsia partialis continua [A.3.b], ictal paresis [A.3.e], nonconvulsive w/o coma, focal without consciousness impairment [B.2.b.a]).

b: distribution of the categories according to the new classification corresponding to focal SE with consciousness impairment (complex partial) in the old classification. Mortality rate was 19.9% for complex partial SE according the old classification, whereas for repeated focal motor seizures (A.3.a) it was 26%, 21.4% for nonconvulsive SE w/o coma, focal with consciousness impairment (B.2.b.c), 11.7% for nonconvulsive SE w/o coma, focal with consciousness impairment (B.2.b.c); and no patient with adversive (A.3.c) or ictal paresis (A.3.e) died.

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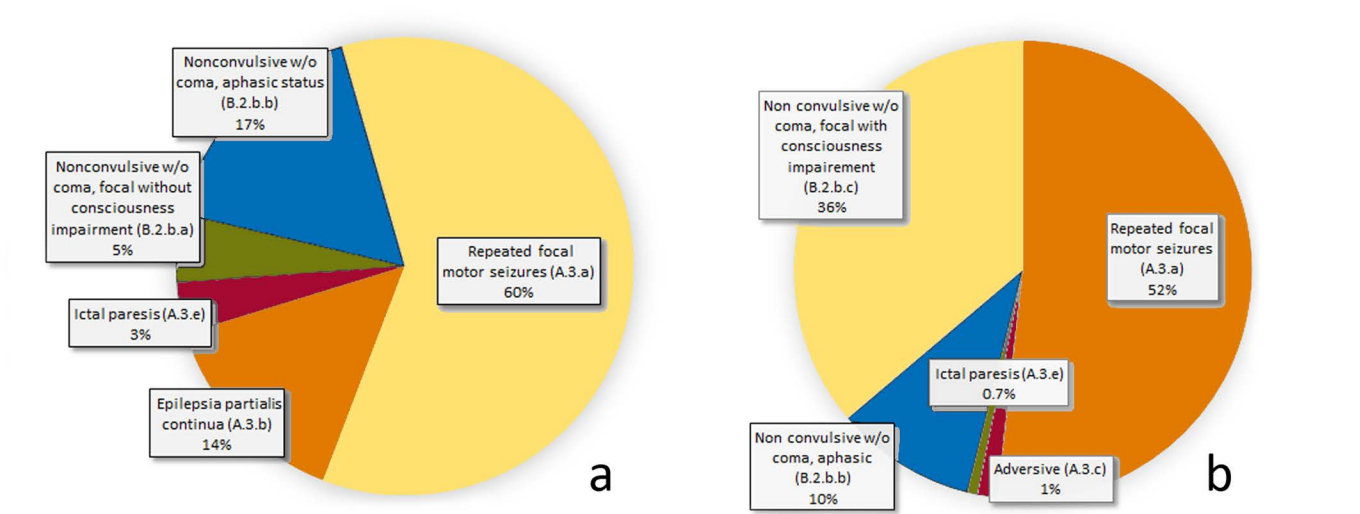
Nonconvulsive w/o coma, aphasic status (B.2.b.b) 17%
Nonconvulsive w/o coma, focal without consciousness impairment (B.2.b.a) 5%
Ictal paresis (A.3.e) 3%
Epilepsia partialis continua (A.3.b) 14%
Repeated focal motor seizures (A.3.a) 60%
a
Non convulsive w/o coma, focal with consciousness impairement (B.2.b.c) 36%
Repeated focal motor seizures (A.3.a) 52%
Ictal paresis (A.3.e) 0.7%
Non convulsive w/o coma, aphasic (B.2.b.b) 10%
Adversive (A.3.c) 1%
b