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State of the Art Approach to the Classification of Epileptic Seizures and Epilepsies

Epileptik Nöbetler ve Epilepsilerin Sınıflamasında Güncel Yaklaşımlar

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ABSTRACT

In the light of the latest knowledge acquired from clinical and laboratory research dealing with genetic, molecular biology and neuroimaging, existing classifications were successively revised by the International League Against Epilepsy (ILAE) in 2001, 2006, and 2010. In the latest classification established in 2010, proposals articulated radical changes in terms of concepts and definitions of the previously published classifications and put forward new classifications for epileptic seizures, epilepsies and electroclinical syndromes. This review refers to the changes of the new classification with their reasons and criticisms. *(Archives of Neuropsychiatry 2014; 51: 189-194)*

Key words: Epilepsy, epileptic syndromes, classification

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ÖZET

Son yıllarda genetik, moleküler biyoloji ve nöro görüntüleme ile ilgili yapılan klinik ve laboratuvar çalışmalarından elde edilen bilgiler ışığında Uluslararası Epilepsi ile Savaş Birliği International League Against Epilepsy (ILAE) tarafından mevcut sınıflamalar sırasıyla 2001, 2006 ve 2010 yıllarında yeniden güncellenmiştir. 2010 yılında yayınlanan son sınıflama önerisinde daha önce yayınlanmış sınıflamalardaki terim ve kavramlarda radikal değişiklikler yapılmış ve epileptik nöbetler, epilepsiler ve elektroklinik sendromlar yeniden sınıflandırılmıştır. Bu derlemede, son sınıflamadaki değişiklikler gerekçeleri ile birlikte ve yapılan eleştirilerle sunulacaktır. *(Nöropsikiyatri Arşivi 2014; 51: 189-194)*

Anahtar kelimeler: Epilepsi, epileptik sendromlar, sınıflama

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Classification systems enable a better understanding of diseases and accompanying symptoms and signs. Objectives in epilepsy classification include unearthing the underlying etiology and planning the therapeutic intervention and prognosis in accordance with the predicted etiology, moreover, in addition to the direct personal benefits in routine clinical practice, it is also aimed at facilitating training, enabling communication among clinicians, providing standard templates for appropriate pre-operative assessment, and relevant scientific research. From a historical perspective, the first classification systems seemed to have been developed on the basis of personal clinical experience. However, the ever accumulating developments deriving from both clinical and laboratory studies imposed the necessity of the periodical update of the classifications by incorporating the relevant information into that, which came from clinical experience. The initial classifications of the International League Against Epilepsy (ILAE) that had been proposed in 1981 and 1989 were deemed to become insufficient due to the later widespread use of video-EEG and the knowledge provided by the developments in molecular biology, genetics and neuroimaging fields (1). This has led to the successive revisions of classification proposals by the ILAE Classification Subcommittees in 2001, 2006, and 2010 that were updated in the light of the latest knowledge (2,3,4,5,6). 2010 proposals articulated radical changes in terms of concepts and definitions of the previously published classifications (Table 1) and put forward new classifications for epileptic seizures (Table 2 and Table 3), epilepsies and electroclinical syndromes (Table 4) (6). Independent from ILAE, Lüders et al. from the Cleveland Clinic had published a semiological seizure classification (SSC) in 1998 (7). Then they proposed a five-axis epilepsy classification scheme in which epilepsy was dealt with as a whole in 2005 (8) and published a revision in 2008 (9). However, each published report continues to create a lively discussion in scientific journals on the subject matter (10,11,12,13,14,15,16,17,18,19,20,21). This review will essentially focus on the ILAE 2010 classification and its criticisms.

In 1989 classification, the definitions of epilepsy and syndrome were used almost interchangeably. Therefore, in the new

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classification proposals, epileptic seizure, epilepsy, and syndrome definitions were modified. According to this final suggestion, "Epileptic Seizure" was defined as temporary symptoms and signs that were observed as a result of the abnormally excessive or synchronous neuronal activity. Epilepsy on the other hand, is a disorder characterized by the persistent predisposition of the brain to create epileptic seizures and this condition causes neurobiological, cognitive, psychological, and social consequences (22). At least one epileptic seizure history is necessary for epilepsy diagnosis. In clinical practice, the classification of the seizure is based on direct observation, on the accounts of an eyewitness informant, or watching a video recording of a seizure. Epilepsy can be accepted as a disease whose symptoms are epileptic seizures. Syndrome is a cluster of symptoms and signs that co-occur and it does not have a single etiology or pathology unlike a disease. Therefore, contrary to epileptic seizures, diagnosis of epilepsy or an electro-clinical syndrome cannot be made by direct observation or watching a video recording. To that end, such additional information as the age of onset, etiology, family history, frequency of seizures, different types of seizures observed in the same patient, precipitating factors, along with ancillary findings from imaging methods and EEG are necessary.

Based on the assumption that the choice of drugs are prompted not by the seizures related to focal epilepsies but only by seizures in generalized epilepsy syndromes (such as absence and myoclonus), ILAE 2010 classification oversimplifies the classification of focal seizures, defining them only according to the degree in the alteration of consciousness (Table 3). They suggested that the division of epileptic seizures as focal or generalized was pragmatic, and when a more detailed explanation was necessary, the seizure semiology dictionary defining ictal findings that was published by ILAE in 2001 should be used (3). The new classification states that the generalized and focal distinction was not needed for the headings of epilepsy and electro-clinical syndromes but for epileptic seizures. In a study by Manford et al., although significant information on seizure symptomatology was obtained from observers for most of the cases, it was reported that epilepsy could not be classified in about one fourth of the patients due to the inability to decide whether the seizures were generalized or focal (23). In spite of the fact that in routine clinical practice, focal seizures may well be observed in generalized seizures and secondary generalized seizures are not infrequent in focal epilepsies (as the occurrence of automatisms or bilateral asymmetrical tonic seizures in juvenile myoclonic epilepsy [JME]), the elimination of generalized/focal distinction, not for the epileptic seizures but for the epilepsies, has been widely criticized by several authors on the grounds that no sufficient scientific evidence was existent for such a radical change (11,12,13,14,15,16,17).

Panayiotopoulos noted that although the generalized and focal seizures/syndromes share pathophysiologic and/or genetic aspects, their differences exceeded their similarities and that the therapeutic errors could be minimized through tackling the said differences (as in the use of carbamazepine for JME or juvenile absence epilepsy) (24).

Although it is true that we need a simple seizure classification for routine clinical practice, thanks to the oversimplification in the last classification, "epilepsy with only generalized tonic-clonic seizures" diagnosis would probably be the most frequent diagnosis according to it and it would be a gross underestimation of the need for a meticulous questioning of the history of the patient for other seizure types, such as the presence of different types of auras, myoclonus and absence that might accompany that type of seizures (11,12,13,14). In some cases, it was observed

Table 1. Major changes of terminology and concepts in classification of epilepsies and seizures

Old terms and concepts	New terms and concepts
etiology	
Idiopathic-possible genetic	Genetic: Genetic defect directly cause epilepsy and seizures are cardinal symptoms of epilepsy
Symptomatic: Due to known or possible brain disease	Structural-Metabolic: Disease as a result of structural or metabolic damage of brain
Cryptogenic: Possible symptomatic	Unknown causes: Due to unknown and genetic-structural or metabolic causes
SEIZURES	
Generalized: First changes show bilateral hemispheric involvement at the beginning	Generalized: As arising in and rapidly engaging bilaterally distributed networks
Focal: First changes show activation of restricted neurons in unilateral hemisphere	Focal: As a result of restricted networks in unilateral hemisphere
Spasms: Not defined	Epileptic Spasms: Focal, generalized or both of them could be seen. They are classified as 'Unknown Causes' because of inadequate evidence
Complex, simple partial, secondarily generalized	Put away old terms. Suggested a dictionary for detailed describing focal seizures by ictal semiology
EPILEPSIES	
Generalized: Epilepsies with generalized seizures	Put away this term
Focal: Epilepsies with focal seizures	Put away this term

*Organized from the reference (Berg AT et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010; 51(Suppl 4):676-685.)

that a precise correspondence does not always exist between the electro-clinical syndromes and their clinical presentation. For instance, infantile spasms and hypsarrhythmia have been classically known as a generalized epilepsy syndrome, however, advances in imaging methods and video-EEG showed us that this condition may occur due to focal cortical dysplasia and surgical excision may enable both seizure control and improve generalized EEG pattern (25,26). Since epileptic spasms can be seen in both focal and generalized epilepsies, ILAE 2010 classification prefers to have it under the "Unknown" heading and adds myoclonic absence and eyelid myoclonus as subgroups (6). However, the "tonic seizures" (e.g., bilateral asymmetrical tonic seizures resulting from the medial frontal discharges) that is similarly likely to be seen in focal epilepsies was left under the generalized seizures heading.

Considering the dynamic character of cerebral functions, anatomic division of the brain into the lobes proves to be insufficient. Since neural networks with complex connectivity patterns do not overlap with rough anatomic boundaries, those boundaries are not enough in defining the clinical presentation of epileptic seizures and instead distinctive spreading styles of seizure activity in the large-scale distributed neural networks must be taken into account in defining the corresponding clinical picture, which arises as a reflection of that particular spread. Seizures displaying similar characteristics may arise from different regions of the cerebral cortex or the same cortical focus may present different seizure characteristics. For instance, in a patient with parieto-occipital epilepsy, either being due to a cortical development abnormality or an infarct, while the seizure presentation may only be the generalized motor seizures, depending upon the spread of seizure activity, visual aura, automotor seizure, focal clonic seizure, or bilateral asymmetrical tonic seizures may well appear individually or in cluster. Based on this observation, 2001, 2006, and 2010 propositions of ILAE insisted on recommending the elimination of the syndromic classification according to anatomic lobes. On the other hand, although it is the underlying factor that is the most important determinant of prognosis in epilepsies, there are some studies that indicate the importance of lesion localization as well. For instance, in a study by Menzler et al., it was demonstrated that the seizure frequency differed due to the same pathologic factor depending upon its localization as in the case of cavernomas (it is higher with mesial temporal compared to extra-mesial temporal involvement) (27). In contrast to this finding, the same lesion localization due to differing pathologic factors may not be the same clinically. In another study, highlighting the importance of the underlying pathology rather than the localization itself, it was shown that the surgical treatment of cavernoma-related mesial temporal epilepsy showed a better outcome compared to hippocampal sclerosis-related mesial temporal epilepsy (28).

Among the most important changes in ILAE 2010 classification is the replacement of the terms 'idiopathic', 'symptomatic', and 'cryptogenic' with 'genetic', 'structural-metabolic', and 'unknown,' respectively, the rationale of which is that these terms may contain different meanings or connotations, that is to say, multiple concepts are being expressed by a single word, and thus, causing confusion. This replacement received a halfhearted acceptance as some authors expressed their concerns that any reason for the replacement of these terms that were sufficiently defined in the ICE (International Classification of Epilepsies and Epileptic Syndromes - proposed by the Commission of ILAE, 1981) classification was not very well-grounded and that the assessment and revision of the accuracy of their meanings would suffice. In the new classification, all cryptogenic and numerous idiopathic epilepsies are compiled under the 'unknown' heading. For instance, deducing from the fact that concordance between siblings being low or non-existent, benign rolandic epilepsy, Panayiotopoulos Syndrome, and Gastaut

Table 2. 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
UNKNOWN
Epileptic spasms

*Reference: Berg AT et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010; 51(Suppl 4):676-685.

Table 3. Descriptors of focal seizures according to degree of impairment during seizures

Without impairment of consciousness or awareness.
With observable motor or autonomic components. This roughly corresponds to the concept of "simple partial seizure".
"Focal motor" and "autonomic" are terms that may adequately convey this concept depending on the seizure manifestations.
Involving subjective sensory or psychic phenomena only. This corresponds to the concept of an aura, a term endorsed in the 2001 Glossary.
With impairment of consciousness or awareness. This roughly corresponds to the concept of "complex partial seizure".
"Dyscognitive" is a term that has been proposed for this concept (Blume et al., 2001).
Evolving to a bilateral, convulsive seizure (involving tonic, clonic, or tonic and clonic components). This expression replaces the term "secondarily generalized seizure."

[a]For more descriptors that have been clearly defined and recommended for use, please see Blume et al., 2001, [b]The term "convulsive" was considered a lay term in the Glossary; however, we note that it is used, *Reference: Berg AT et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010; 51(Supll 4):676-685.

Table 4. Electroclinical syndromes and other epilepsies

Electroclinical syndromes arranged by age at onset[a]
Neonatal period
Benign familial neonatal epilepsy (BFNE)
Early myoclonic encephalopathy (EME)
Ohtahara syndrome
Infancy
Epilepsy of infancy with migrating focal seizures
West syndrome
Myoclonic epilepsy in infancy (MEI)
Benign infantile epilepsy
Benign familial infantile epilepsy
Dravet syndrome
Myoclonic encephalopathy in nonprogressive disorders
Childhood
Febrile seizures plus (FS+) (can start in infancy)
Panayiotopoulos syndrome
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)[b]
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 myoclonic epilepsies (PME)
Autosomal dominant epilepsy with auditory features (ADEAF)
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
Hemiconvulsion-hemiplegia-epilepsy
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 vs. focal)
Epilepsies attributed to and organized by structural-metabolic causes
Malformations of cortical development (hemimegalencephaly, heterotopies, etc.)
Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber, etc.)
Tumor
Infection
Trauma
Angioma
Perinatal insults
Stroke
Etc.
Epilepsies of unknown cause
Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy
Benign neonatal seizures (BNS)
Febrile seizures (FS)

a The arrangement of electroclinical syndromes does not reflect etiology, b Sometimes referred to as Electrical Status Epilepticus during Slow Sleep (ESES), *Reference: Berg AT et al. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010; 51(Supll 4):676-685.

type of childhood occipital epilepsy syndrome were classified under the 'unknown' heading. However, the subcommittee notes in another section that "…genetic factors are likely to play a role in these syndromes", and this statement support the classification of these syndromes as 'idiopathic' as it was the case in the previous classifications rather than as 'unknown' reasons. In order to eliminate the concerns with the term 'symptomatic', such as the conception that all epilepsies are ultimately somehow symptomatic and that one of its connotations is bad prognosis, this term was replaced with 'structural-metabolic'. Structural lesions include such genetic causes as tuberous sclerosis and cortical developmental malformations, in addition to acquired causes such as stroke, tumor, and infection. However, despite the existence of the epilepsies related to autoimmune, degenerative, toxic, inflammatory or neurochemical changes, some of which may well be without structural or metabolic causes, these were not mentioned in the classification and this has attracted rightful criticism (29). Subcommittee also noted the need for sub-classifications for both structural and metabolic causes in the long run. Thanks to the rapid developments in genetic studies within recent years, forming a new group named 'genetic' epilepsies was quite appropriate and was widely accepted. However, some authors supported its inclusion not as a replacement but as an addition to conventional trichotomy of 'idiopathic', cryptogenic', and symptomatic groups (29,30,31). Conceptual elimination of the term idiopathic generalized epilepsy and the replacement of the term genetic will not be able to fill in the gaps in our present state of knowledge. Conversely due to a particular causal genotype may present with various epileptic phenotypes and epilepsies because of not only a structural abnormality like a cortical dysplasia but also multiple genotypes may cause trouble for classification. For instance, mutations in the ARX gene is both causative of a phenotype: West syndrome and a structural abnormality: lissencephaly (11,12,13,14,15,16,17). As in the case of familial autosomal dominant focal epilepsies, some epilepsies may readily be included in the genetic heading just as in ILAE 2001 and 2006 classifications. However, some other epilepsies such as childhood absence, JME, and Rolandic epilepsy await further confirmation.

The new classification declares that there is no need to insist on making a distinction between disease and syndrome, and epilepsy syndromes are only mentioned by their names instead of their defining features. However, the expectation from the subcommittee was to confirm or deny the syndromes that were defined with the evidence available at the time in 1989 classification and to revise them in more detail if needed.

Syndromic classification may not be always possible or syndrome diagnoses may sometimes be quite rigid in clinical practice so that it may not be possible to squeeze in the entire set of findings into one syndromic framework. In a study, it was reported that only 4% of adult cases and 21% of children had a syndromic diagnosis according to ILAE classification, even at a tertiary epilepsy center, and the authors concluded that case-oriented individual approach would be more beneficial in classifying a heterogeneous disease with various etiologies such as epilepsy (26). In a five-axis classification suggested by Lüders et al., it was highlighted that it would be more suitable to position the individual cases "in an organized frame" in practice and that it would be beneficial for the sub-categories within the said organized frame to be inter-related and flexible (32).

In the new classification, "catastrophic" and "benign" terms were also eliminated. It was believed that the term "catastrophic" was not appropriate to use in diagnostic classification due to its emotional load. A benign epilepsy syndrome is characterized by epileptic seizures, which do not necessitate treatment, which have a good treatment response, or which remit without sequelae. The term 'benign' in general medical terminology is often used for conditions that are not progressive, repetitive and malignant, that can recover, and that do not necessitate lifelong treatment. It is well known that whatever the reason may be, epilepsy can be accompanied by sudden death, cognitive loss, behavioral disorders, and suicide. Based on this, the subcommittee refrained from the use of the term "benign epilepsy" and suggested instead the term "responsive to treatment". However, this also brings along some issues. Firstly, at least one third of childhood epilepsies require no treatment at all. Secondly, responses of patients with the same disease to treatment may differ. In children with Rolandic epilepsy and in benign childhood syndromes, there may be linguistic, other cognitive, and behavioral abnormalities that are generally mild and reversible; those rare cases harboring those abnormalities in a more severe or irreversible manner are still debated if they are secondary to antiepileptic drugs, the underlying cause and/or the social stigmatization attached to the diagnosis of epilepsy.

Furthermore, the last two classifications of ILAE consider the age of onset, unlike the previous classifications. This approach was also attracted criticism as it contrasted with the classification efforts of other diseases in neurology in particular and in medicine in general.

Berg responded to criticisms on behalf of the organization in July 2012 in the journal Epilepsia (33) and noted that they had not been expecting a ready acceptance and implementation of a radically new classification system that attempts to take the place of the previous ones (i.e., 1981 and 1989 ILAE classifications) which had been being widely used for a long time, including being incorporated within the International Classification of Diseases (ICD). However, Berg noted that some of the criticisms were unfair, that different researchers, such as epidemiologists, neurosurgeons, and genetic scientists were criticizing the classification from the viewpoint of the priorities of their own fields, and thus, the organization was not in a position to accept these criticisms in their entirety (33). Birbeck notes in his own criticism that any classification system should be flexible and multidimensional enough in order not to be a factor for loss of motivation for future studies (34). However, how this is going to be precisely realized, how the evidence-base of the information that is used while developing the classification system is going to be ensured and how such insurance is going to be improved while the new evidence comes out is debatable. At the 2011 American Epilepsy Society meeting, scientists and clinicians from various parts of the world have been commissioned in quite a wide scope for ICD-11 classification projects.

Epileptic seizures appear on a fundamental epileptogenic susceptibility (genetic) ground and with the effect of triggering factors and in addition in some cases, with direct causal factors;

therefore, clinician can be of help to her patients to the extent of her ability to clarify such factors. Unfortunately, our current knowledge has been far from lucid for a complete understanding of the pathogenetic mechanisms of epilepsies. As also noted by the subcommittee, commissioning scientists from such various fields as clinical practice, epidemiology, and genetic science for the new classification proposals can lead to a more satisfactory classification that is both scientifically updated by the incorporation of the new developments and also practical for the clinical usage.

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