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Summary

The current classification of the epilepsies and epileptic syndromes is practical and useful in a majority of cases. However, the choice of its subdivisions was mainly derived from adult data, and its applicability is frequently problematic in early childhood. This article reviews some issues related to the classification of epilepsies in childhood and summarizes recent proposals that might improve the current scheme.

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Problèmes liés à la classification des épilepsies chez le jeune enfant

La classification actuelle des épilepsies et syndromes épileptiques est pratique et utile dans une majorité de cas. Cependant, le choix de ses subdivisions étant basé sur des données principalement recueillies chez l'adulte, son utilisation chez le jeune enfant est souvent problématique. Cet article passe en revue certaines difficultés liées à la classification des épilepsies chez l'enfant, et résume quelques propositions récentes ayant pour but d'améliorer le schéma actuel.

Mots-clés : Epilepsie, classification, enfance

Probleme mit der Klassifikation der Epilepsien in der frühen Kindheit

Die aktuelle Klassifikation der Epilepsien und Epilepsie-Syndrome ist praktisch und in den meisten Fällen nützlich. Ihre Unterteilung folgt jedoch aus Erwachsenen-Daten, und ihre Anwendung bei Kindern kann problematisch sein. Dieser Artikel beschreibt einige dieser Schwierigkeiten und fasst neue Klassifikations-Vorschläge zusammen.

Schlüsselwörter: Epilepsie, Klassifikation, Kindheit

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Introduction

The utility of classifying diseases has been recognized for a long time in all medical disciplines. Indeed, an adequate classification improves communication between observers, helps to understand underlying pathophysiological mechanisms, to guide the selection of appropriate diagnostic investigations and treatments, and to give prognostic indications to the families. From a wider standpoint, it improves the quality of care given to the patient. Such a tool is particularly useful in conditions like the epilepsies, in which etiology, treatment and prognosis vary along a very wide clinical spectrum that includes benign idiopathic epilepsies that do not require any treatment on one end, and intractable symptomatic epilepsies associated with severe mental retardation on the other end.

The first proposal for an international classification of the epilepsies was made by Gastaut in 1969, on behalf of the International League Against Epilepsy (ILAE) [1]. The ILAE adapted this initial scheme in 1989 [2]. However, despite recent extensive advances in various diagnostic procedures, which have led to the identification of new epileptic syndromes and to a better delineation of others, the 1989 classification has not yet been modified accordingly. Moreover, although its various subcategories are particularly adapted to adult epilepsies, its use in infancy is often difficult.

The aim of this review is to present some issues with the current classification of the epilepsies, and particularly those related to its applicability in early-childhood. Future perspectives are also discussed.

Issues with the use of the 1989 ILAE Classification of Epilepsies and Epileptic Syndromes in infancy

The 1989 ILAE classification of Epilepsies and Epileptic Syndromes was proposed to supplement the International Classification of Epileptic Seizures proposed in 1981 [3]. The latter was limited by the fact that describing solely seizures without additional fundamental aspects, such as precipitating factors, etiology, or age of onset, rarely occurs among colleagues, and does not help in terms of treatment choices or prognosis. It was therefore necessary to develop a tool that would be practical and allow useful communication between physicians dealing with seizures and epilepsy.

The epilepsy classification is based on a major dichotomy: the generalized or focal character of the seizures. Epilepsies with focal seizures (as defined by semiology

or investigations) are considered as localization-related (focal) epilepsies and those with generalized seizures (i.e., with initial clinical manifestations indicating involvement of both hemispheres, and bilateral ictal electroencephalographic changes at onset) as generalized epilepsies. The epilepsies are further divided into subcategories, based on their etiology: Symptomatic epilepsies are a direct consequence of a known or suspected disorder of the central nervous system (CNS). Idiopathic epilepsies are those in which no identifiable cause is known. They are presumed to be genetically determined. Cryptogenic epilepsies are “presumed to be symptomatic, but the etiology is not known” [3].

Those epilepsies in which both generalized and focal seizures coexist, and those in which the generalized or focal character of seizures is impossible to assess, are classified in the “undetermined whether focal or generalized” category.

Finally, special syndromes such as febrile seizures or isolated seizures are also recognized as a separate category.

This classification scheme is applicable to a great number of epilepsies, including in childhood. In a prospective, community-based study, Berg et al. demonstrated that a specific epilepsy syndrome diagnosis could be assigned to the majority of the 613 children included [4].

Nevertheless, some issues derived from this proposal exist, most of which were already recognized at the time of its publication [2]. Some of them are of particular relevance in early childhood.

First, patients may move from one category to another during their evolution. This is particularly true for infants, whose brain anatomy and physiology mature over time. For example, it is well known that a certain proportion of children with West syndrome later develop seizures and EEG characteristics consistent with Lennox-Gastaut syndrome. A similar evolution might also be observed in patients who present in the neonatal period with one of the recognized epileptogenic encephalopathies (Early Infantile Epileptogenic Encephalopathy, Early Myoclonic Epilepsy), and West syndrome later in their first year of life.

Second, attributing a syndrome name does not mean that its underlying etiology is similar from one patient to another. West syndrome can be idiopathic or caused by various CNS abnormalities, such as tuberous sclerosis or focal cortical dysplasia, for instance. Treatment choices, seizure control prediction, and developmental prognosis are obviously very different in all of these situations.

Third, seizures in children, and particularly in those less than 2 years, have specific characteristics that make their categorization in the current scheme difficult. The most relevant of them in terms of epilepsy classification in this age group, is the fact that focal and generalized seizures frequently coexist in the same child, as in Dravet syndrome, for example. Moreover,

the clinical presentation of seizures in infancy does not always correlate well with its electrographic correlate [5]. In particular, tonic seizures and behavioral arrest seizures, two types of events frequently observed under the age of 2 years, might look clinically generalized but exhibit ictal focal abnormalities on EEG [5]. Similarly, infants with focal anatomical CNS abnormalities might present with bilateral symmetric seizures, such as spasms. The categorization of these events is therefore extremely difficult in the absence of a good quality video-EEG recording, which might not always be readily available. Finally, in the rare Malignant Migrating Partial Seizures of Infancy [6], focal seizures have the peculiarity to start independently in a nearly continuous way in different areas of the brain. They are associated with severe mental retardation. In the rare published series on this syndrome, no consistent brain abnormality has been described on cerebral imaging. This suggests diffuse brain dysfunction, possibly caused by a metabolic defect, as yet unidentified. Categorizing this entity is obviously difficult.

As a result of what precedes, an important number of young epileptic patients cannot be accurately classified and end up in heterogeneous categories, for which treatment options are ill-defined and prognostic indications are missing. Approximately one quarter of a group of 140 children with cryptogenic or idiopathic epilepsy could not be classified according to the current scheme [7]. In another study on epilepsies in infants (< 2 years), one third of the syndromes were classified as “Undetermined whether focal or generalized” [8]. All of these aspects underline the need for a classification more adapted to infants. One possibility would be to further divide these broad categories into more specific and homogeneous subgroups. This could help identify new epileptic syndromes likely to be caused by metabolic or genetic defects [8].

Genetics

Major genetic advances have been made recently, and have added most useful information in the comprehension of the pathophysiological mechanisms underlying some forms of epilepsies. The current classification antedates by several years these findings, which were therefore obviously not included in the scheme.

In some cases, the discovery of genetic abnormalities has completed the identification of epileptic syndromes previously diagnosed on the sole basis of specific clinical manifestations. This is the case for Benign Familial Neonatal Convulsions, associated with numerous mutations in the gene coding for two subunits of a potassium channel, *KCNQ2* and *KCNQ3* [9], and for Dravet syndrome, in which various abnormalities in the gene coding for the subunit of a sodium-channel, *SCN1A*, have been identified [10].

In addition to their role in the diagnosis of epileptic

syndromes, genetic analyses will hopefully provide valuable prognostic indications. Mutations in the gene coding for the pore region of the abnormal sodium-channel have been shown to be more frequent in typical Dravet syndrome than in less severe phenotypes, for instance [11]. Similarly, truncation mutations in the sodium-channel 1A gene are more frequently associated with Dravet syndrome than missense mutations [12].

Finally, the increasing knowledge in the field of pharmacogenetics provides hope for a major improvement in the treatment of epilepsy. In addition to their potential use in the development of new anti-epileptic drugs, genetic tests could identify which drugs would most likely control seizures in specific situations, what dosages should be used, and which patient would be a good epilepsy surgery candidate [13-15].

Despite these advances, the relationship between genotype and phenotype remains incompletely understood in most epilepsies. Nevertheless, these data highlight the potential major contribution of genetics in the future management of epilepsy. It also underlines the need to further delineate homogeneous epilepsies subgroups, in order to perform genetic research with increased specificity, and the necessity to include such fundamental information in the classification, when available, in the aim of preparing the future.

The 2001 ILAE diagnostic scheme and other proposals

Because of all the above-mentioned changes, the ILAE stated that a review of the 1989 classification was necessary [16]. However, it was unanimously agreed upon that the current proposal “should not be discarded, unless a clearly better classification would be devised” [17]. This has not been the case, so far. Instead of elaborating a potentially more rigid and complex classification, the ILAE proposed a diagnostic scheme based on five axes (ictal semiology, seizure type, epileptic syndrome, etiology, and degree of impairment), and on lists of recognized seizure types and epileptic syndromes [16-17]. The list of epilepsy syndromes is based on age of onset and related conditions. This scheme is not intended to replace the former classification, but rather aims at precisely describing individuals with epileptic conditions [17]. Its practical use and applicability is under evaluation.

Others proposed a “neurological, patient-oriented” approach to a new epilepsy classification, supposed to be more practical and adaptable to the additional information sometimes obtained in the course of the disease [18]. It is based on five dimensions (epileptogenic zone, seizure semiology, etiology, seizure frequency, and related medical information). This scheme differs mainly from previous proposals by the fact that epilepsy syndromes, that are sometimes vaguely defined and lack biological homogeneity, are not an essential component

of the classification. As the authors themselves state, this proposal might not be as well-adapted to childhood epilepsies, most of which are best managed with a syndrome approach. This proposal also awaits further evaluation.

To attribute specific syndromes in childhood, we propose to add data to the lists proposed by the ILAE [17], such as development at onset, prominent seizure types (semiology) and interictal EEG results. This simple and practical approach would eliminate the difficulty of classifying cases into idiopathic versus symptomatic, or generalized versus focal categories. It should be sufficiently efficacious to at least restrict the list of possible epilepsy syndromes, if not specifically identify one of them, in a majority of epileptic children. For instance, a 1 week-old hypotonic baby presenting with myoclonias and suppression-burst trace probably has Early Myoclonic Encephalopathy. A 6 month-old normal child presenting with prolonged febrile convulsions and interictal generalized spike-and-waves is likely to have Dravet syndrome. A nine month-old child with severe developmental delay, frequent partial seizures and multifocal interictal spikes probably has Malignant Migrating Partial Seizures of Infancy, and so on. The mentioned data are summarized for some well-described syndromes in **table 1**.

Conclusion

Classifying epilepsies is a fundamental tool in the management of patients. The current ILAE epilepsy classification is practical, and useful in most situations. However, its applicability in early childhood is not optimal, and there is a definite need for improvement in this particular group of age. Several proposals have been made that are currently under evaluation.

References

1. Gastaut H. Classification of the epilepsies. Proposal for an international classification. *Epilepsia* 1969; 10(Suppl): 14-21
2. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989; 30: 389-399
3. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981; 22: 489-501
4. Berg AT, Shinnar S, Levy SR, Testa FM. Newly diagnosed epilepsy in children: presentation at diagnosis. *Epilepsia* 1999; 40: 445-452
5. Korff CM, Nordli DR Jr. The clinical-electrographic expression of infantile seizures. *Epilepsy Res* 2006; 70(Suppl 1): S116-S131
6. Coppola G, Plouin P, Chiron C et al. Migrating partial seizures in infancy: a malignant disorder with developmental arrest. *Epilepsia* 1995; 36: 1017-1024
7. Sarisjulis N, Gamboni B, Plouin P et al. Diagnosing idiopathic/cryptogenic epilepsy syndromes in infancy. *Arch Dis Child* 2000; 82: 226-230

Table 1. Summarized characteristics of some epilepsy syndromes in infancy

Age at onset	Development/Neurological examination	Prominent seizure type	Interictal EEG	Syndrome
Neonatal period	Normal	Clonic or tonic-clonic	Normal or “thêta pointu alternant”	BFNS / BNFNS
	Abnormal	Tonic	Suppression-burst	Ohtahara
	Abnormal	Clonic	Suppression-burst	EME
Infancy	Normal	Behavioral arrest or focal, in series	Normal	BIS
	Normal, or mildly delayed	Clonic	Normal	MEI
	Normal, then severely delayed	Febrile focal clonic, then multiple types	Focal and generalized spike-and-waves, central rhythmic theta	Dravet
	Severely delayed	Nearly continuous, clonic	Multifocal spikes	MPSI
	Delayed	Spasms	Hypsarrhythmia	West
Childhood	Normal or mildly delayed	Clonic or myoclonic-astatic	Normal or generalized spike-and-waves or polyspike-waves, central rhythmic theta	MAE
	Normal	Absences	Normal, or isolated generalized spike-and-waves	CAE
	Normal	Focal motor	Rolandic spikes	BCECTS
	Delayed	Nocturnal tonic, atypical absences	Slow spike-and-waves	LGS
Adolescence	Normal	Absences	Normal or generalized polyspike-and-waves	JAE
	Normal	Myoclonic	Normal or generalized polyspike-and-waves	JME

Abbreviations: BCECTS, benign childhood epilepsy with centrotemporal spikes; BFNS, benign familial neonatal seizures; BIS, benign infantile seizures; BNFNS, benign non-familial neonatal seizures; CAE, childhood absence epilepsy; EME, early myoclonic encephalopathy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; LGS, Lennox-Gastaut syndrome; MEI, myoclonic epilepsy in infancy; MAE, myoclonic-astatic epilepsy; MPSI, migrating partial seizures of infancy

8. Korff CM, Nordli DR Jr. Epilepsy syndromes undetermined whether focal or generalized in infants. *Epilepsy Res* 2006; 70(Suppl 1): S105-S109
9. Singh NA, Westenskow P, Charlier C et al. BFNC Physician Consortium. *KCNQ2 and KCNQ3 potassium channel genes in benign familial neonatal convulsions: expansion of the functional and mutation spectrum. Brain* 2003; 126: 2726-2737
10. Dravet C, Bureau M, Oguni H et al. Severe myoclonic epilepsy in infancy: Dravet syndrome. *Adv Neurol* 2005; 95: 71-102
11. Kanai K, Hirose S, Oguni H et al. Effect of localization of missense mutations in *SCN1A* on epilepsy phenotype severity. *Neurology* 2004; 63: 329-334
12. Claes L, Ceulemans B, Audenaert D et al. De novo *SCN1A* mutations are a major cause of severe myoclonic epilepsy of infancy. *Hum Mutat* 2003; 21: 615-621
13. Depondt C. The potential of pharmacogenetics in the treatment of epilepsy. *Eur J Paediatr Neurol* 2006; 10: 57-65
14. Depondt C, Shorvon SD. Genetic association studies in epilepsy pharmacogenomics: lessons learnt and potential applications. *Pharmacogenomics* 2006; 7: 731-745
15. Ferraro TN, Dlugos DJ, Buono RJ. Challenges and opportunities in the application of pharmacogenetics to antiepileptic drug therapy. *Pharmacogenomics* 2006; 7: 89-103
16. Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001; 42: 796-803
17. Engel J Jr. Report of the ILAE classification core group. *Epilepsia* 2006; 47: 1558-1568
18. Loddenkemper T, Kellinghaus C, Wyllie E et al. A proposal for a five-dimensional patient-oriented epilepsy classification. *Epileptic Disord* 2005; 7: 308-320

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