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EDITORIALS

Diagnostic Approach of Epilepsy in Childhood and Adolescence

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ABSTRACT

Epilepsy diagnosis in childhood and adolescence should follow the general neurological principles of diagnostic approach. Latest advances in neuroimaging and genetics determined International League Against Epilepsy (ILAE) to promote new terminologies and concepts for organization of seizures and epilepsies. This review presents the current approach to epilepsy diagnosis in childhood and adolescence using the five axis system and recent revisions proposed by ILAE.

Keywords: epilepsy, diagnosis, childhood, adolescence

INTRODUCTION

The Epilepsies are chronic neurological disorders characterized by a predisposition for recurrent epileptic seizures; the heterogeneity of the entities in this group is obvious today. The pharmacological choices (need for treatment, type of drug), duration of treatment, the non-pharmacological approach (epilepsy surgery, ketogenic diet) and other general recommendations depend on the type of epileptic syndrome and on the etiology of epilepsy. Correct diagnosis has practical consequences: optimal therapeutic choice and appreciation of the epilepsy outcome.

Incidence of epilepsy is higher in pediatric population comparing with adults (excepting senior population), consequently there is a high probability in daily practice for general practitioners and pediatricians to consult patients with epilepsy. The aim of this paper is to help the trainees and young specialist to understand the present diagnostic approach of the epilepsy in childhood and adolescence. ❑

TERM DEFINITIONS

The Commission on Epidemiology and Prognosis (CEP) of the International League Against Epilepsy (ILAE) proposed conceptual and operational definitions of epilepsy and other paroxysmal events. These terms were established by consensus (1), initially in 1993, to provide a common language in the epidemiological, clinical and therapeutical studies and

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for the daily practice. Some term definitions were questioned during last years, and conceptual modifications were proposed (2). In 2011 CEP – ILAE published a document promoting consistency in methods and definitions (3). We present the useful terms in daily clinical practice:

Epileptic seizure – „a transient occurence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" – 2005 (2). „The clinical manifestation consist of sudden and transitory abnormal phenomena which may include alterations of consciousness, motor, sensory, autonomic, or psychic events, perceived by the patient or an observer" – 1993 (1).

Status epilepticus – „a single epileptic seizure of more than 30-min duration or a series of epileptic seizures without resumption of baseline central nervous system functions interictally lasting more than 30-min" – 1993 (1).

Epilepsy – operational definition – is still recommended for epidemiological studies. According to this definition epilepsy is „a condition characterized by recurrent (two or more) epileptic seizures, unprovoked by any immediate identified cause. Multiple seizures occuring in a 24-h period are considered a single event. An episode of status epilepticus is considered a single event" – 1993 (1). The 2005 concept (2), defined epilepsy as „a disorder characterized by an enduring predisposition to generate epileptic seizures and by a neurobiologic, cognitive, psychological and social consequences of this condition. The definition requires the occurence of at least one epileptic seizure". This concept is more difficult to manage, consequently it is considered that epilepsy should be recognized by any pshysician but the epilepsy diagnosis should be established by physicians with epileptology expertise.

Nonepileptic events – „clinical manifestations presumed to be unrelated to an abnormal and excessive discharge of a set of neurons of the brain, including: disturbances in brain function (vertigo or dizziness, syncope, sleep and movement disorders, transient global amnesia, migraine, enuresis) and pseudoseizures (nonepileptic sudden behavioral episodes presumed to be of psychogenic origin; these may coexist with true epileptic seizures)" – 1993 (1). ❑

Focal seizures = originating within networks limited to one hemisphere	**Characteristics that can be used for classification:** **1. the degree of impairment during the seizure** - without impairment of consciousness or awareness - with observable motor or autonomic features - involving subjective sensory or psychic phenomena only - with impairment of consciousness or awareness - evolving to a bilateral, convulsive seizures
	2. ictal semiology and localization - frontal lobe - temporal lobe - parietal lobe - occipital lobe - multilobar - with characteristics that do not allow localization
	3. depending on the basic clinical events and their sequence of appearance
Generalized seizures = originating at some point within, and rapidly engaging bilaterally distributed networks	**Types of generalized seizures:** - tonic-clonic (in any combination) - absences - typical - atypical - absences with special features: - myoclonic absences - eyelid myoclonia - myoclonic - myoclonic - myoclonic atonic - myoclonic tonic - clonic - tonic - atonic
Unknown = impossible to define the seizures as focal or generalized based on current knowledge, therefore they are grouped separately	- epileptic spasms

TABLE 1. Schematic definition and classification of epileptic seizures, as recommended by ILAE, 2010.

EPILEPSY DIAGNOSIS

For correct and complete analysis and classification of signs and symptoms the principles of the neurological diagnosis should be followed: what? (clinical diagnosis), where? (topographical diagnosis), and why ? (etiological diagnosis) (4). A detailed history, complete general clinic and neurologic examination, diagnostic hypothesis and wise choice of complementary evaluations are all important elements for epilepsy diagnosis (5).

The use of the 5-axis diagnosis, published in 2001 (6) is very useful. Adapted to daily prac-

tice and using also the new concepts and terminology proposed in 2010 by the Commission of Classification and Terminology (CCT) of ILAE (7), these axis are:

Axis 1 – are the paroxysmal events epileptic seizures? (to be diferentiated from nonepileptic events). If epileptic, the seizures semiology should be described, according to the terms from the Glossary published by ILAE in 2001 (8).

Axis 2 – define type of seizures: focal, generalized or unknown if focal or generalized (epileptic spasm belong to this last category). If focal seizures, attempts to define lateralization and localization should be done.

Axis 3 – syndrome diagnosis (electroclinical syndromes are epilepsies with particular clinical and electroencephalographic (EEG) features allowing their recognition; syndrome diagnosis is important for therapeutic approach and prognosis estimation).

The following features should be described: age of onset, description of seizure semiology, relation to sleep, precipitant factors, motor and cognitive development, neurological exam and the EEG features.

Axis 4 – etiologic diagnosis (genetic, structural – metabolic or unknown). Detailed description should follow.

Axis 5 – description of associated deficits. ❑

THE VALUE OF CLASSIFICATION AND NEW CONCEPTS FOR ORGANIZATION

The latest proposal of the CCT - ILAE in 2010 may represent a step forward in terms of concepts organization in epilepsy. It had been preceded by other proposal which referred to the organization of electroclinical syndromes, in 2001 (6). The purpose of the revised terminology and concepts for organization of seizures and epilepsies is to allow flexible organization of the epilepsies and active integration of neuroscience discoveries into daily practice. It is increasingly clear at this point that the classifications of epileptic seizures (9), from 1981 and of epilepsies and epileptic syndromes (10), from 1989, no longer fulfill their purpose of organizing epilepsies, due to the supplementary scientific knowledge available today.

Some concepts for classification of epileptic seizures (axis 2) were simplified (Table 1).

Epilepsies are further classified using axis 3, which refers to whether the clinical and elec-

Electroclinical syndromes arranged by age of onset	**= clinical entities that are identified by a cluster of electroclinical characteristics**
	Neonatal period - Benign familial neonatal epilepsy - Early myoclonic encephalopathy - Ohtahara syndrome
	Infancy - Febrile seizures plus (FS+) - Benign infantile epilepsy - Benign familial infantile epilepsy (BFIE) - West syndrome - Dravet syndrome - Myoclonic epilepsy in infancy (MEI) - Myoclonic encephalopathy in nonprogressive disorders - Epilepsy of infancy with migrating focal seizures
	Childhood - Febrile seizures plus (FS +) - Early onset childhood occipital epilepsy (Panayiotopoulos syndrome) - Epilepsy with myoclonic atonic (previously astatic) seizures - Childhood absence epilepsy (CAE) - 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 (LGS) - Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS) - Landau-Kleffner syndrome (LKS)
	Adolescence - Adult - Juvenile absence epilepsy (JAE) - Juvenile myoclonic epilepsy (JME) - Epilepsy with generalized tonic – clonic seizures alone - Autosomal dominant epilepsy with auditory features (ADEAF) - Other familial temporal lobe epilepsies
	Variable age at onset - Familial focal epilepsy with variable foci (childhood to adult) - Progressive myoclonus epilepsies (PME) - Reflex epilepsies
Distinctive constellations / surgical syndromes	**= characteristic clinical entities related to specific lesions or other causes; their recognition is important due to their therapeutical implications, particularly surgery**
	- Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS) - Rasmussen syndrome - Gelastic seizures with hypothalamic hamartoma - Hemiconvulsion-hemiplegia-epilepsy

TABLE 2. Electroclinical syndromes and distinctive constellations, as recommended by ILAE (2010, 2011).

trographic features allow recognition of a specific electroclinical syndrome or not, and axis 4, which refers to identifying a specific etiology or not.

The electroclinical syndromes are arranged by the age of onset and they are not grouped in focal or generalized anymore (Table 2).

Proposed terms to describe the causes of epilepsies try to eliminate the previous ambiguities and to allow the use of new scientific findings. The etiology of epilepsy can be genetic, structural / metabolic or unknown (according to present knowledge). These terms replace the previous categories idiopathic, symptomatic or cryptogenic (Table 3).

CCT - ILAE thus proposes a new way of thinking organization of epilepsies, more pragmatic: seizures may be part of an electroclinical syndrome or not, and can have genetic, structural or metabolic causes or can be of unknown cause (11). ❑

THE VALUE OF COMPLEMENTARY EVALUATIONS

Investigations should be asked with clear purpose, in an individualised manner.

- Electroencephalogram (EEG) is recommended for the diagnosis of epileptic seizure (axis 1), type of seizure (axis 2) and electroclinical syndrome (axis 3), sometimes giving clues for etiology (axis 4). A normal EEG does not exclude epilepsy diagnosis. An EEG with epileptiform discharges in a child without seizures or cognitive or language regression does not establishes the diagnosis of epilepsy. 5-8% of normal children may have epileptiform discharges on the EEG (12,13).

- Cerebral imaging may reveal the etiology of epilepsy (axis 4), (may show structural abnormalities in some cases). An identified lesion may or may not be the cause of epilepsy. It is important to correlate the type of seizure and estimated origin (localization) from clinical and EEG informations and the identified lesion. Most often the neuroimagistic evaluation is not an emmergency (14). The Committee for Neuroimaging of ILAE published guidelines for imaging infants and children with recent-onset epilepsy (15). Not all the cases are to be imaged (Table 4), but when needed, MRI is the choise of election.

- Genetic testing and identifying the predisposition genes for epilepsy are important for both research and clinical practice (17). Mutations analysis and their neurophysiological and neurodevelopmental effects may contribute to understanding the seizure susceptibility processes. This may further contribute to new AEDs (antiepileptic drugs) development or finding remedies against pathophysiologic mechanisms of epilepsy (antiepileptogenic treatments). Genetic testing may clarify etiologic diagnosis (axis 4) and may predict the risc for epilepsy of in families with positive epilepsy history. More than 20 genes with role in epilepsy susceptibility have been described. One of the most valued discoveries for the epilepsy diagnosis was for example the SCN1A gene, involved in most cases of Dravet syndrome (severe epileptic encephalopathy characterized by prolonged hemiclonic seizures triggered by fever in infants less than 1 year). This electroclinical syndrome has particular: response to several AEDs, prognosis and associated disorders.

- Metabolic testing may also contribute to the etiologic diagnosis of epilepsy (axis 4) – for example demonstration of high levels of pipecolic acid (indirect biomarker) in plasma and CSF (18) and of alpha-aminoadipic semialdehyde in urine and plasma (specific biomarker with some exceptions) (19) in pyridoxine-dependent epilepsy support the diagnosis, which can be further confirmed by genetic testing and demonstration of antiquitine (ALDH7A1) mutations (20). Other clinical evaluations, beside initial neurological and neurodevelopmental evaluation: psychiatric, ophtalmological, hearing, as well as psychological testing contribute to defining the associated impairments (axis 5). Ideally these should be done since the initial diagnosis for a full assessment of children and adolescents with epilepsy (21). ❑

Old concepts and terms	Recommended new concepts and terminology
Idiopathic: presumed genetic	*Genetic:* genetic defect directly contributes to the epilepsy, and seizures are the core symptom of the disorder
Symptomatic: secondary to a known or presumed disorder of the brain	*Structural-metabolic:* caused by a structural or metabolic insult or disorder of the brain
Cryptogenic: presumed symptomatic	*Of unknown cause:* the cause is unknown; it might be genetic, structural or metabolic

TABLE 3. Epilepsy etiologies – concept and terminology changes between former (1981, 1989) classifications and terminologies and the newly proposed Terminology and Concepts (2010).

CONCLUSION

Epilepsies are fairly common in pediatric practice and extensive information over the last years may overwhelm the trainees and young specialists. Listen the parents and the patient carefully, examine the child rigorously and follow a coherent diagnostic algorithm with well-defined objectives and in collaboration with other specialties. This approach will allow the epilepsy diagnosis to be in accordance with current knowledge in the field in a significant proportion of cases, and small patients to receive the most appropriate treatment for their disease. ❑

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Following electroclinical syndromes: 1. Childhood absence epilepsy 2. Juvenile absence epilepsy 3. Juvenile myoclonic epilepsy 4. Benign epilepsy with centro-temporal spikes (BECTS) (to be noted: approximately 15% of children with BECTS may have an abnormal MRI, but the structural abnormalities described do not alter the favorable prognosis of epilepsy (16).
NB: - Brain MRI is recommended in patients with known non-lesional syndromes when atypical features are associated (abnormal neurological / intellectual development, resistance to treatment, atypical course of epilepsy). - Current evidence does not support recommendations on other non-lesional electroclinical syndromes: childhood epilepsy with occipital paroxysms, primary reading epilepsy, benign neonatal seizures, myoclonic epilepsy in infancy, reflex epilepsies.

TABLE 4. Situations where imaging may not be necessary, ILAE 2009.

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