THE EPILEPTIC ENCEPHALOPATHY JUNGLE: FROM DR WEST TO THE CONCEPTS OF AETIOLOGY-RELATED AND DEVELOPMENTAL ENCEPHALOPATHIES

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PURPOSE OF REVIEW
We aim to further disentangle the jungle of terminology of epileptic encephalopathy and provide some insights into the current understanding about the aetiology and pathophysiology of this process. We cover also the key-features of epilepsy syndromes of infancy and childhood which are considered at high risk of developing an epileptic encephalopathy.

RECENT FINDINGS
The concept of ‘epileptic encephalopathy’ has progressively been elaborated by the International League Against Epilepsy (ILAE) according to growing clinical and laboratory evidence. It defines a process of neurological impairment caused by the epileptic activity itself and therefore potentially reversible with successful treatment, although to a variable extent. Epileptic activity interfering with neurogenesis, synaptogenesis and normal network-organisation as well as triggering neuroinflammation are among the possible pathophysiological mechanisms leading to the neurological compromise. This differs from the newly introduced concept of ‘developmental encephalopathy’ which applies to where the epilepsy and developmental delay are both due to the underlying aetiology and aggressive antiepileptic treatment may not be helpful.

SUMMARY
The understanding and use of correct terminology is crucial in clinical practice enabling appropriate expectations of antiepileptic treatment. Further research is needed to elucidate underlying pathophysiological mechanisms, define clear outcome predictors and find new treatment targets.

KEYWORDS
Epilepsy, cognitive impairment, epileptic encephalopathy, developmental encephalopathy, childhood, epilepsy syndrome
KEYPOINTS

- Epileptic encephalopathy describes a concept where the epileptic activity contributes significantly to the cognitive and behavioural impairment regardless of aetiology, type of epilepsy and age.

- Developmental encephalopathy describes conditions where the seizures and developmental impairment occur together and are an epiphenomenon of the underlying aetiology.

- Successful treatment of epileptic activity may improve or reverse cognitive impairment in an epileptic encephalopathy, but aggressive treatment should be avoided with a developmental encephalopathy.

- Grouping various heterogeneous electroclinical epilepsy syndromes of infancy and childhood as “the epileptic encephalopathies” is confusing for clinicians and research and should be avoided.

- Additional studies are needed to elucidate aetiology and pathophysiological mechanisms in epileptic encephalopathy and provide targeted treatment.
INTRODUCTION

In 1841, in his letter to the editor of Lancet, Dr West of Tunbridge was the first to describe an epileptic encephalopathy, writing about a particular type of epilepsy affecting his young child, now well-known as the syndrome that took his name when the triad of epileptic spasms, hypsarrhythmia and developmental plateauing or regression are present [1]. Dravet conceived then the term ‘epileptic encephalopathy’ in her thesis in 1965 to relate to the concept that the abundant epileptic activity contributes to the neurodevelopmental impairment in the now known Lennox-Gastaut Syndrome [2]. In their proposal of 2001 [3], the International League Against Epilepsy (ILAE) commission for classification included several electroclinical syndromes with onset in early childhood and poor prognosis in terms of seizure control and neurodevelopmental outcome in the category of epileptic encephalopathies (EE) of infancy and childhood. Moreover, in this report the term ‘epileptic encephalopathy’ appeared also as a concept, further redefined by Berg et al in 2010 [4] as where the epileptic activity itself contributes to the severe cognitive and behavioural impairments above and beyond what might be expected from the underlying pathology alone. The global or selective impairments may worsen over time and might be seen at any age, along a spectrum of severity and across all epilepsies.

This concept has critical implications on the management of these patients leading to the presumption of reversibility of the neurodevelopmental comprise and to the premise of a need to treat aggressively [5**]. However, in their most recent paper the ILAE acknowledge the important but not exclusive role of epileptic activity in causing the disturbance of cerebral function [6]. The trend is now to describe aetiology-related encephalopathies applied for instance to a single gene disorder such as CDKL5. Furthermore, the concept of ‘developmental encephalopathy’ is introduced by Scheffer et al to distinguish conditions where the epilepsy and the developmental problems are rather an epiphenomenon of the underlying cause and the latter are not caused above and over by the seizures or the interictal epileptic activity themselves.

In this review, we aim to provide an overview of the jungle of epileptic encephalopathies discussing further the old and new concepts of epileptic and developmental encephalopathies, as well as the current understanding of possible related pathophysiological mechanisms.
THE GROUP OF THE EPILEPTIC ENCEPHALOPATHIES OF INFANCY AND CHILDHOOD

Various electroclinical syndromes are included in the group of the so called epileptic encephalopathies (EEs) of infancy and childhood. An electroclinical syndrome is defined by the age of onset of the epilepsy, the clinical presentation and the associated electroencephalographic features. The idea behind clustering and labelling specific electroclinical syndromes as EEs of infancy and childhood was to highlight the increased risk for this group to develop an 'encephalopathic' effect irrespective of aetiology [4]. However, this may not affect all of the patients included in this category. It should be also pointed out that applying the same term to a process as described before and to a specific category of epilepsy syndromes is confusing for clinical utility and research [7]. Table 1 summarises the clinical features, known aetiologies and proposed treatments for these electroclinical syndromes as well as typical EEG and brain imaging findings when present [8*, 9-16, 17**, 18].

THE EPILEPTIC AND DEVELOPMENTAL ENCEPHALOPATHY - WHAT WE KNOW AND WHERE WE ARE STILL IN THE DARK

In this section we refer to epileptic encephalopathy (EE) as a concept where the epileptic activity in form of frequent seizures and/or interictal epileptic discharges (IEDs), impacts adversely on brain function contributing significantly to cognitive, behavioural and/or motor plateauing or regression [4]. This definition has been derived from both clinical and laboratory evidence. In a prospective community-based study in children with early onset epilepsy, Berg et al [19] found a worse developmental outcome with diagnostic delays, thus when children had been exposed longer to the epileptic activity. In another prospective study, Berg et al [20] showed that uncontrolled seizures impair cognitive function and emphasised the importance of early and effective treatment. The devastating consequences of ongoing seizures with worse neurodevelopmental outcome are highlighted by the association of longer delay between onset of spasms and treatment demonstrated in West syndrome [21-23]. Another argument frequently found in the literature to sustain the concept of epileptic encephalopathy is that children with previously normal development show language or more global cognitive/behavioural impairment of brain function after seizure onset and/or the appearance of abundant epileptiform discharges in slow-wave sleep as it is the case in LKS and CSWS respectively [24]. Furthermore, in the animal model recurrent seizures during early development are associated with pronounced long-term deficits in spatial learning and memory, tested with the Morris and radial-arm water maze models, and impaired social behaviour [25, 26].
There are numerous reports of potential reversibility of the neurodevelopmental compromise with successful treatment of the seizures in children [27, 28] and these findings underscore the negative influence of epileptic activity on brain function. Even in adulthood, an improvement in cognitive performance might be seen after achieving better seizure control, as observed in two adult patients with Dravet syndrome by Catarino et al [29]. However, evidence now suggests also that there is not a linear relationship and cognitive recovery may be limited despite achieving seizure freedom and/or normalisation of the EEG [30-32]. Nonetheless, it is noteworthy that a catch-up may be observed only years after a successful treatment [33].

The exact pathophysiological mechanisms of how epileptic activity causes the neurodevelopmental compromise remain largely uncertain. IEDs may have a transient interference with cognitive processing or more long-lasting effects in the involved brain areas and also in those areas distant from the epileptic focus but connected to each other [34*, 35]. In a very recent study with intracranial EEG monitoring in adults, Ung et al elegantly demonstrate the nociferous influence of IEDs outside the epileptic onset zone on memory encoding and retrieval [36*]. A more enduring adverse consequence could be presumed when frequent interictal spiking occurs and the epileptic network interferes with the cognitive networks, as suggested by the results of functional neuroimaging studies on some specific electroclinical syndromes [37]. The maturational state of the brain when aggressed by the epileptic activity is undoubtedly important, as age-dependent plastic processes are affected. In the rodent-model which had been exposed to early seizures, the subsequent increased seizure susceptibility and higher vulnerability to the seizures’ devastating effects on cognition and behaviour in adulthood, have been related to altered neurogenesis, synaptic reorganisation and disruption of the normal network-organisation. Furthermore, emerging evidence highlights the role of neuroinflammation in the immature brain which can be permanently modified due to the inflammatory insult. Neuroinflammation is presumed to be a common pathway in response to various brain insults including seizures, and to act subsequently as a promotor of seizure recurrence, cognitive and behaviour impairment. A pathological mutual perpetuation between seizures and neuroinflammation might arise, leading to a progressive decline of the neurological impairment. Genetic and epigenetic factors may dysregulate one or the other component of this vicious pathological cycle. Interestingly, in the animal models the innate immune response of the central nervous systems involving immune cells (astrocytes, microglia), cytokines, chemokines and related activated inflammatory cascade molecules, is age-dependent. Moreover, in contrast to the adult, no neuronal death is evident in the neonate rodent-model after recurrent and/or
prolonged seizures. This might explain in part the variability of clinical patterns, such as age-specific electroclinical syndromes [38, 39, 40*, 41, 42**].

This year the ILAE officially introduced the term of ‘developmental encephalopathy’ to describe conditions where the epilepsy and the cognitive impairment may occur together and the contribution of other factors such as aetiology is likely to be more important than the epileptic activity itself in determining the neurological impairment [5]. It is crucial to recognise a ‘developmental component’ where present, to manage expectations from seizure treatment, with regard to the neurological compromises as the latter are at least in part not reversible. This is also helpful to limit fruitless aggressive treatment of seizures considering the potential additional harmful adverse effects of antiepileptic drugs (AEDs) on behaviour and cognition. In Dravet syndrome, for example, the developmental slowing often precedes the period of frequent seizures and abnormal EEG [43]. However, this does not exclude an EE component in the course of Dravet syndrome. Finally, it is often difficult to determine the extent of negative influence of the epileptic activity and decide on escalation of seizure treatment aiming for a better neurodevelopmental outcome. The latter is remarkably poor in the so called early epileptic encephalopathies with suppression burst pattern and seizures are extremely refractory to treatment. Nevertheless, it is still unclear whether a better seizure control with new future treatment would yield an improvement of the current poor prognosis [6].

With the current advances in genetics, an increasing number of genes such as *CDKL5, STXBP1* and *KCNQ2* have been linked to the group of electroclinical epilepsy syndromes in infancy and childhood at high risk of developing an epileptic encephalopathy [8, 44, 45]. In future this may be advantageous when tailored treatment for genetic mutations might become available. However, the use of the term ‘gene-related encephalopathies’ is controversial as there is not a straightforward genotype-phenotype correlation and often a wide clinical spectrum is seen with the same mutation even within the same family. Thus, the developmental and epileptic component of the ‘gene-related encephalopathy’, when present, can be variable. Prediction of the clinical course from the mere known mutation is therefore still not possible and ultimately not helpful for the clinician. On the other hand, the same electroclinical syndrome can be caused by mutations in different genes. This is not to discourage aetiology research, which remains essential, but to take aetiology into account as one, but not the principal factor influencing the clinical course.
The advances in determining the genetic landscape of the early onset epilepsies, have changed our overall approach to their investigation, providing in many a diagnosis and consequent closure for the families. At presentation, EEG recording (with preferably documentation of seizures) and epilepsy protocol MRI may give clues to syndrome and underlying aetiology respectively. Genetic investigations may be dictated thereafter by clinical course (eg Dravet) or MRI (eg Tuberous sclerosis). In onset under three years, the question arises as to the role of metabolic investigation, but this again may be driven by the clinical picture. Treatable metabolic causes such as pyridoxine and biotinidase deficiencies should be considered early inevitably, next generation sequencing, increasingly through multiple gene panel evaluation, leads to more rapid and accurate diagnosis, ultimately in some leading to an interventional change in management eg ketogenic diet in SLC2A1 mutations, enzyme replacement in CLN2 disease. Such diagnosis however more commonly will currently direct genetic counselling as well as expectations with regard to prognosis.

CONCLUSION

It was pivotal to finally disentangle the jungle of terminology, and we endorse the proposition of the ILAE to use the term ‘epileptic encephalopathy’ when referring to the concept that an epileptic process causes neurological impairment and lessening the epileptic activity might improve outcome. Further, the presence of a developmental component as described by the ILAE and caused by seizure-independent factors should be researched and recognised. The use of correct terminology enables appropriate expectations of treatment, ascertains avoidance of senseless overtreatment of epileptic activity, and is crucial for future research. There is still a need to find clear outcome predictors and markers for treatment response to help clinicians to decide on treatment strategies. Research should also continue to further elucidate pathophysiological mechanisms and aetiology in epileptic encephalopathy. This may open for new treatment strategies to prevent and/or reverse long-term neurological impairment by targeting the involved neurobiological processes.

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Pharma and Eisai, and as speaker for Shire, Zogenix, and GW Pharma, again for which remuneration was made to her department. She holds grants from the European Union, National Institute for Health and Research (NIHR), Action Medical Research, Great Ormond Street Hospital Charity and SPARKS. This work was supported by the NIHR Great Ormond Street Biomedical Research Centre.

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**This book fully explore the epilepsy-aphasia spectrum discussing exhaustively the relationship between epilepsy, neurological, and developmental aspects of language, cognition, and sleep based on the long clinical experience of the authors**


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