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PLENARY, PARALLEL AND DISCUSSION SESSIONS

Epileptic encephalopathies of infancy

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Abstract

The paper briefly review the concept of epileptic encephalopathy. Three age-dependent epileptic encephalopathy in infancy, i.e. Ohtahara syndrome, West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome were outlined, particularly stressing the developmental aspects. Extreme intractability of these syndromes requires further elucidation of their pathophysiologies and urgent therapeutic development.

INTRODUCTION

A diagnostic scheme for people with epileptic seizures and with epilepsy proposed by ILAE Commission (2001)[1] newly adopted the concept of "epileptic encephalopathy" as one of new key terms. It is defined as a condition in which epileptiform abnormalities are believed to contribute to the progressive disturbance in cerebral function, but this definition may be ambiguous.

The proposal include 8 syndromes; early myoclonic encephalopathy, Ohtahara syndrome, West syndrome, Dravet syndrome, myoclonic status in non-progressive encephalopathies, Lennox-Gastaut syndrome, Landau-Kleffner syndrome, epilepsy with continuous spike-waves during slow-wave sleep. To these syndromes, the migrating partial seizures in infancy and severe epilepsy with multiple independent spike foci[2] may be reasonably added.

"Catastrophic epilepsy" is also a collective term for types of childhood epilepsy that take a highly unfavorable course despite intensive treatment, often with polypharmacy (Kramer).[3] This is understood almost synonymous with epileptic encephalopathy.

In this brief review, epileptic encephalopathies will be dealt in the following concept: a particular group of usually age-related and extremely intractable epilepsies with characteristic generalized minor seizures and massive epileptic EEG abnormalities, both of which cause stagnation/deterioration in mental and cognitive functions in addition to the pre-existing developmental deficit due to organic brain damage.

AGE-DEPENDENT EPILEPTIC ENCEPHALOPATHY

In 1978, I proposed the age-dependent epileptic encephalopathy that consists of Ohtahara syndrome, West syndrome and Lennox-Gastaut syndrome. Its definition and conception are somewhat different from that of epileptic encephalopathy in ILAE proposal, but of course, the age-dependent epileptic encephalopathy should be included and take the special position in this new category.[4,5]

EPILEPTIC ENCEPHALOPATHIES OF INFANCY

Of the 656 children with epilepsy under 15 years of age who initially visited our hospital, 100 children had onset within 6 months of life. This included 40 children with localization-related epilepsies, 32 were symptomatic, 8 cryptogenic, and none idiopathic. In those with generalized epilepsies, West syndrome was diagnosed in 34 children, Ohtahara syndrome in 2 and early myoclonic encephalopathy in 4. Ten of the 20 children of undetermined group had Dravet syndrome.

DEVELOPMENTAL ASPECTS

From the developmental viewpoint, evolutional changes among syndromes are most important.[5-7] This characteristic is most typically manifested in the age-dependent epileptic encephalopathy with mutual transition among its 3 syndromes. Twelve out of 16 children with Ohtahara syndrome evolved to West syndrome with age, and those Ohtahara syndrome children consist of 2.6% of West syndrome. Its transition to West syndrome mostly occurred after 3-4 months of age. One

hundred and seven out of 231 children (59.3%) with West syndrome evolved to Lennox-Gastaut syndrome in the late infancy. Inversely, 36% of Lennox-Gastaut syndrome had a history of West syndrome. The mutual transition strongly suggests the close relationship, supposedly based on common pathophysiology, among the three syndromes, and supports the inclusive concept of the age-dependent epileptic encephalopathy.[6] Considering the heterogeneous underlying pathologies, the age factor is the common denominator responsible for the manifestation of characteristic clinical and electrical features of each syndrome. Accordingly, these epileptic encephalopathies may be the age-specific epileptic reaction to various non-specific exogenous brain insults acting at specific developmental stages.

Transition of Lennox-Gastaut syndrome to severe epilepsy with multiple independent spike foci (MISF) after adolescence is also noticeable. This syndrome is extremely intractable and new therapeutic developments or break-through is strongly desired.[2]

DIFFERENTIATION BETWEEN OHTAHARA SYNDROME AND EARLY MYOCLONIC ENCEPHALOPATHY

As the malignant neonatal epileptic syndromes with suppression-bursts in EEG, Ohtahara syndrome and EME may be diagnostically controversial.[7,8] The decisive importance of the developmental viewpoint should be stressed for the differentiation or delineation of syndromes, though it is a very laborious work.

Decisive difference in the interictal EEG findings of both syndromes is well known; suppression-bursts are consistently observed in both waking and sleeping states in Ohtahara syndrome, but those of early myoclonic encephalopathy appear only in deep sleep or become more apparent in sleep.

Developmentally, suppression-bursts in Ohtahara syndrome evolves to hypsarrhythmia around 3-4 months of age, and sometimes further to diffuse slow spike-waves. Whereas, in early myoclonic encephalopathy suppression-bursts may persist up to late childhood after a transient evolution to hypsarrhythmia in the middle to late infancy. Transition between syndromes is also specific; Ohtahara syndrome evolves to West syndrome, and further to Lennox-Gastaut syndrome with age, but early myoclonic encephalopathy persists long without such evolution except for a transient phase of West syndrome.[9]

DRAVET SYNDROME

The clinical characteristics include a family history of epilepsy or febrile seizures, normal development before onset, generalized or unilateral alternative febrile clonic seizures beginning during the first year of life, following appearance of myoclonic jerks, atypical absences and often partial seizures. In spite of frequent severe clinical seizures, intensive EEGs fail to disclose epileptic discharges in infancy. Thereafter, generalized spike-waves and polyspike-waves, photo- and pattern sensitivity, and focal abnormalities begin to appear. Psychomotor development stagnates from the second year of life on, and interictal myoclonus may appear. Treatment is extremely difficult. Myoclonic seizures, atypical absences and partial seizures decrease with age, but generalized convulsive seizures persist, usually during sleep.

Recently reported gene abnormality, that is de novo mutations in the sodium-channel gene SCN1A, indicates the possibility of channelopathy of this syndrome.[10]

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