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What is Lennox-Gastaut syndrome in the modern era?

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Abstract

Lennox-Gastaut syndrome was the first established epileptic syndrome to promote the concept of syndromic classification based on the combination of special clinical pictures and EEG findings. Later, several borderline types of epilepsies were separated from Lennox-Gastaut syndrome, specifying different epileptic syndromes. Regarding the etiology of Lennox-Gastaut syndrome, diffuse pathological gray matter lesions of a heterogeneous origin appear to play a major role. However, slow progress has been made to elucidate the pathophysiology underlying Lennox-Gastaut syndrome.

INTRODUCTON

Lennox and his coworkers first described clinical correlations of fast and slow spike-and-waves (SW) in 1950, in which they showed a unique combination of brain damage, atypical seizure types, and a poor prognosis in the slow SW group.[1] Then, 16 years later, Gastaut and his colleagues published a commemorable article entitled "Childhood epileptic encephalopathy with diffuse slow SW or Lennox syndrome".[2] They extensively studied the clinical and EEG correlations and established Lennox syndrome as a distinct electro-clinical epileptic syndrome. They also described the triad of this syndrome, which are still major criteria of Lennox syndrome: 1) frequent tonic seizures, and a variant of petit mal absence, later re-designated as atypical absence seizures; 2) pronounced homogeneous mental retardation; 3) interictal EEG recordings showing pseudo-rhythmical (1.5-2.5 c/s) diffuse slow SW. Later, astatic or drop attacks and paroxysmal fast activity in the sleep EEG were added to these criteria. Thus, the syndrome has been termed Lennox-Gastaut syndrome (LGS) in recognition of the contributions of these two great epileptologists.

Another very important aspect of this syndrome not described in detail by Lennox *et al* and Gastaut *et al* is marked, age-dependent change in clinical and EEG manifestations, extensively studied by Ohtahara and his coworkers in the early 1980s.[3] They established the earliest form of epileptic encephalopathy, known as Ohtahara syndrome, and demonstrated the evolution from Ohtahara syndrome to West, and from West to LGS in the same child. They stressed that cerebral maturation is responsible for this marked age-dependent change.

DIFFERENTIAL DIAGNOSIS OF LENNOX-GASTAUT SYNDROME

The differential diagnosis of LGS from other known epileptic syndromes mostly fulfilling one or two criteria of LGS is important in clinical practice. They comprise atypical benign partial epilepsy of childhood, epilepsy with continuous spike-wave during slow sleep (CSWS), focal epilepsies with secondary bilateral synchrony, idiopathic myoclonic-astatic epilepsy in early childhood, and progressive myoclonus epilepsies (PME). Atypical benign partial epilepsy of childhood was first described by Aicardi and Cherie in 1982[4], sharing the clinical and EEG features of epilepsy with CSWS and focal epilepsies with secondary bilateral synchrony. Atypical benign partial epilepsy of childhood is characterized by: 1) epilepsy onset between 2 and 6 years, 2) normal development prior to onset, 3) more than 2 types of seizure (focal motor and atonic, or atypical absence seizures), 4) centro-temporal (C-T) EEG spikes during wakefulness and CSWS, and 5) good seizure and mental prognoses. Patients with atypical benign partial epilepsy of childhood first develop focal motor seizures and CT-EEG spikes, and later combine drop attacks and diffuse slow SW EEG during sleep. As compared with typical generalized slow SW EEG in LGS, they show both C-T focal spikes and diffuse slow SW with a lateralizing amplitude predominance suggestive of secondary bilateral synchrony.[5] They never experience generalized tonic seizures or tonic drop attacks.

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As for the differential diagnosis from idiopathic myoclonic-astatic epilepsy in early childhood, there is controversy regarding the distinction of this syndrome from cryptogenic LGS. Although idiopathic myoclonic-astatic epilepsy in early childhood patients show myoclonic-astatic or atonic drop attacks, they never exhibit tonic drop attacks or generalized tonic seizures.[6] PME may present clinical and EEG pictures resembling those of LGS sometime during the clinical course, but they usually exhibit progressive and deteriorating neurological pictures.

With respect to the etiology of LGS, it is heterogeneous similarly to West syndrome. We investigated the etiology of 72 cases of LGS followed up for longer than 10 years, in which 21 cases were cryptogenic and the remaining 51 were symptomatic.[7] Twenty-four cases (33%) evolved from West syndrome. The recent progress in cytogenetical and molecular biological analysis has revealed a few specific chromosomal abnormalities or mutations of the gene causing characteristic epileptic syndromes. Patients with a large inv dup (15) containing PWACR are characterized by mental/growth retardation, epilepsy, behavioral problems, and dysmorphism. They have epileptic spasms, generalized tonic seizures, atypical absence seizures, complex partial seizures, and manifest with West syndrome and LGS. Supernumerary marker chromosomes contain UBE3A, GABRB3, and GABRA5 which can affect the excitation of CNS neurons.[8] Patients with band heterotopia, known as double cortex syndrome caused by mutation of the doublecortin gene, sometimes show LGS.[9] Thus, diffuse pathological gray matter lesions of a heterogeneous origin can cause LGS.

The neurophysiological mechanism underlying absence epilepsy involving 3-Hz spike-waves was elegantly elucidated by Gloor and his coworkers, demonstrating that mild genetically-determined cortical hyperexcitability interacting with the spindle-inducing thalamo-cortical system produces a 3-Hz spike-wave.[10] Recently, Steriade and Amzica became the first to experimentally produce generalized slow SW and runs of fast activity in an anesthetized cat, and revealed that a cortically-generated slow oscillation mechanism naturally giving rise to the physiological K-complex generates these characteristic EEG patterns in the presence of pathological gray matter lesions.[11]

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