Inflammatory theory of diseases

What has it got to do with late-onset LGS?

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Lennox-Gastaut syndrome (LGS) is the most common epileptic encephalopathy in children presenting between 3 and 5 years of age. It is a complex age-related epilepsy syndrome with multiple possible etiologies such as hypoxic ischemic injuries, genetic syndromes, cerebral cortical malformations, and tumors. The etiology may remain elusive in approximately 25% of the cases.¹ Similar to many other childhood epilepsy syndromes, the age at onset can be variable but can be delayed into adulthood. LGS is characterized by multiple seizure types, abnormal EEG characteristics, and cognitive decline. Nonconvulsive status epilepticus, previous diagnosis of West syndrome, earlier age at onset, and a symptomatic etiology are the known independent risk factors for progressive neuropsychological decline. Multiple seizures types, such as tonic-atonic drop attacks, tonic seizures, focal impaired awareness seizures, atypical absences, myoclonic seizures, focal to bilateral tonic-clonic seizures, or generalized seizures, can be encountered. Diffuse generalized slowing, generalized paroxysmal fast activity of 10–20 Hz mainly during non-REM sleep, and slow spike and slow wave (<2.5 Hz) are some of the electroencephalographic hallmarks of this syndrome. Both pediatric and adult epileptologists are well familiar with the diagnostic challenges and delays and medical intractability of LGS. Brain MRI can help clinicians to exclude focal or diffuse structural abnormalities. Genetic/chromosomal DNA microarrays are other diagnostic tools because the disease lacks any biomarkers. Double-blind, placebo-controlled studies have found lamotrigine, valproic acid, topiramate, felbamate, clobazam,² rufinamide,³ and cannabidiol⁴ to be effective. Other treatment options include ketogenic diet, vagal nerve stimulation, corpus callosotomy, anterior thalamic stimulation, or even resection of focal lesions.⁵

Smith et al.⁶ and his group from Mayo clinic screened 453 consecutive patients retrospectively and identified 10 rare cases of late-onset LGS. Their inclusion criteria were multiple seizure types including tonic-atonic seizures, inpatient video EEG monitoring with comprehensive epilepsy evaluation, and the electroclinical syndrome of LGS ≥ 10 years. The age at onset ranged from 10 to 32 years, with a mean age of 16.5 years. Surprisingly, 8 of 10 patients were females, although several previous studies have indicated a slight male predominance in LGS. All patients met the criteria of medically intractability. The average number of failed antiseizure drug trials ranged 7–16. Two patients had a family history of seizures. One patient had “febrile-related” seizures. Seven of 10 patients had a normal MRI. Two patients had cortical malformations, and the third patient had colpocephaly. Two of their patients had a history of acute lymphoblastic leukemia (ALL) as young children. Both patients with ALL were given intrathecal methotrexate, and 1 patient was treated with cranial radiation. Other CSF parameters such as nucleated cell count, oligoclonal bands, and immunoglobulin G indices were normal. Limited genetic mutations and autoimmune epilepsy panels were obtained to rule out progressive myoclonic epilepsies, Dravet syndrome, Doose syndrome, and other autoimmune epilepsies. The authors recognized that ictal activity itself can cause elevation of protein and lactate levels with even reactive pleocytosis in CSF. Tumani et al.⁷ conducted a study focusing on ictally-induced CSF parameters in 151 patients and showed that ~60.9% patients showed elevation of noninflammatory high CSF protein (mean 107 mg/dL) and lactate levels, which did not have any indication of pathologic

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implications. They excluded patients with meningitis, encephalitis, or meningeal carcinomatosis. The elevated CSF protein level was significantly associated with male sex, generalized seizures, and older age.

There is no doubt that this study has several limitations such as a very small cohort size and observational and retrospective study design. Some other interesting well-studied childhood epilepsy syndromes such as Rasmussen encephalitis and Landau-Kleffner syndrome may share the same theory of inflammation. Only 5 patients of 10 had a spinal tap. What were the indications of spinal tap in those 5 patients and why it was deferred in other 5 patients remain unclear to readers. Most patients had daily seizures. However, seizure burden in patients with persistent seizures was not clarified. Are we seeing the effect of frequent seizures as a cause of increased CSF protein levels? Further studies are needed to see whether their findings can be replicated. Inflammatory conditions can also cause hypoglycorrhachia, which was not reported in this study. It is well known that intrathecal chemotherapy with methotrexate and cytarabine arabinoside (Ara-C) can definitely cause mild arachnoiditis causing blockage of CSF flow and high proteins to a frank chemotherapy-induced myelopathy. Do anti-inflammatory drugs have any role to play in this syndrome as they do in Landau-Kleffner syndrome or infantile spasms? It remains to be seen.

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