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Clinical Observations

Pharmacoresistent Partial Epilepsy Secondary to Progressive Inflammatory Poliodystrophy

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ABSTRACT

BACKGROUND: Epilepsy with progressive cortical volume loss is described secondary to energy failure such as mitochondrial disorders, infectious, or inflammatory etiologies and associated with temporal lobe epilepsy. Postmortem studies do not support that spontaneous seizures even if present for prolonged periods universally result in cortical volume loss. **MAIN FINDINGS:** We describe two children with extratemporal pharmacoresistent epilepsy, slowly progressive gray matter volume loss over several years, and evidence of central nervous system inflammation. Brain magnetic resonance imaging changes and antibody profiles were not typical of a well-defined, antibody-mediated central nervous system syndrome such as N-methyl-D-aspartate receptor encephalitis. **CONCLUSIONS:** These patients illustrate a novel presentation of a subacute inflammatory central nervous system process with epilepsy and progressive cortical volume loss, supporting the role of sequential brain imaging in children with epilepsy.

Keywords: Poliodystrophy, pharmacoresistant epilepsy, autoimmune encephalitis, paraneoplastic encephalitis, Rassmusen encephalitis

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Background

Epilepsy is caused by a broad range of inherited or acquired conditions. The clinical history, in combination with an electroencephalograph and structural imaging of the brain by magnetic resonance imaging are useful in determining the underlying etiology and classification of epilepsy. Classification helps guide medication management and provide prognosis.

Symptomatic epilepsy is frequently caused by brain malformations or remote injuries diagnosed by the pattern of brain involvement on magnetic resonance imaging: white matter, gray matter, or a combination. For example, in a child with a history of prematurity, periventricular white matter injury suggests remote perinatal ischemic injury as the risk factor for epilepsy. Progressive gray matter volume loss occurs secondary to energy failure from mitochondrial disease. Infectious, inflammatory, and vascular processes typically affect both gray and white matter.

The natural history of structural changes further narrows the possible etiologies. Most symptomatic epilepsy is caused by a remote monophasic process such as a birth injury or a brain malformation that, once identified, negates the need for further imaging. Processes associated with progressive structural changes such as mitochondrial diseases, Rassmussen encephalitis, or infectious and inflammatory encephalitis have a monophasic acute progressive natural history. A subgroup of patients with temporal lobe epilepsy

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developed slowly progressive degenerative temporal lobe volume in the amygdala and entorhinal cortex as a consequence of febrile seizures or prolonged duration of epilepsy.[1,2] Postmortem examinations of patients with refractory generalized and partial epilepsy do not support gray matter volume loss as a universal process.[3] In animal models of epilepsy, hippocampal volume changes correlated with severity of injury leading to epilepsy, but were independent of number of spontaneous seizures.[4] A poorly defined subgroup of patients with temporal lobe epilepsy developed chronic mesial volume loss over a long interval.[1,2]

Here we describe two children who presented with pharmacoresistant epilepsy initially thought to be secondary to a distant monophasic process that then progressed over years with denuding of the cortex, evidence of inflammation, and response to immunomodulation.

Patient Descriptions

Patient 1

This 9-year-old right-handed Asian boy presented with complex partial seizures with secondary generalization. His birth history, early developmental milestones, and family history were unremarkable. His initial neurological examination was normal and electroencephalography showed left posterior quadrant epileptiform discharges. Brain magnetic resonance imaging done at age 9 years (Fig 1) showed diffuse volume loss with cortical thinning and gliosis within the left cerebral hemisphere, most prominently in the frontal operculum which was consistent with a previous hemispheric ischemic event, possibly even prenatal. Seizures persisted despite treatment with herbal medications, valproic acid, oxcarbazepine, levetiracetam, and zonisamide.

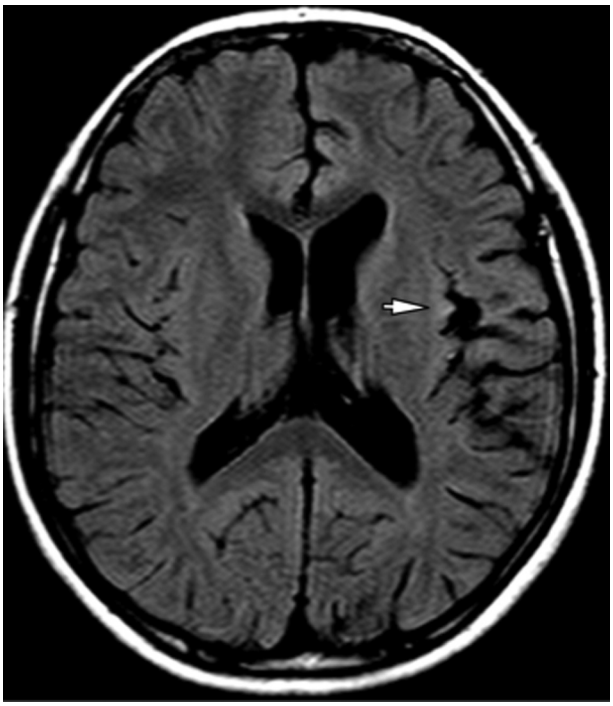

FIGURE 1.
Patient 1. Baseline magnetic resonance imaging at 9 years old. T2 axial fluid-attenuated inversion recovery. The left lateral ventricle is enlarged and the Sylvian fissure is prominent. There is left hemispheric cortical thinning and focal cortical hyperintensity (arrow). These changes were initially thought to represent an old middle cerebral artery territory ischemic injury with atrophy and gliosis.

At age 12 years, video electroencephalograph captured multiple seizures consisting of a behavioral arrest. The electroencephalograph showed focal onset in the left posterior quadrant electrodes with variable spread patterns. Repeat magnetic resonance imaging at age 12 (Figs 2-4) of the brain showed progressive loss of gray matter just above the calcarine fissure on the left side with subtle progressive widening of sulci in the left occipital region, suggesting ongoing volume loss. His neurological examination remained normal. Neuropsychiatric evaluation showed a decline between 10 and 12 years with progressive worsening of verbal working memory, recall, and expressive language recall. Routine studies performed on lumbar puncture were normal including oligoclonal bands, lactate, pyruvate, and neurotransmitters. Chromosome microarray and mitochondrial genome testing were negative for known mutations. Systemic markers of inflammation and thyroid studies were negative. Cerebral angiogram showed no evidence of vasculitis. A paraneoplastic antibody panel was abnormal with striational acetylcholine antibodies (1:240 with normal range< 1:60). Whole body computed tomography imaging for tumor was negative. Intravenous immunoglobulin was initiated, 1 mg/kg 1 day per month for 1 year without further deterioration in brain magnetic resonance imaging or further neuropsychiatric decline. Seizures persisted despite intravenous immunoglobulin. He was tried on phenytoin and clobazam and went into prolonged remission with the addition of lamotrigine. Intravenous immunoglobulin was stopped after 1 year with the patient in seizure remission on lamotrigine. Magnetic resonance imaging of the brain was repeated 1 year after intravenous immunoglobulin was stopped, which showed progression of volume loss with rare brief seizures recurring (Fig 5).

Patient 2

This 4-year-old left-handed Hispanic girl presented with Jacksonian seizures beginning in the left leg with secondary generalization. Her birth history, development, and family history were negative for risk factors for epilepsy. Her neurological examination was normal. Initial electroencephalography showed frequent multifocal epileptiform discharges with right hemisphere predominance. Magnetic resonance imaging at age 4 years (Fig 3) of the brain showed multiple foci of gray matter thinning in the right hemisphere, which was thought to be secondary to an old ischemic event. Levetiracetam led to increasing seizures, and the patient was switched over to valproic acid, which was associated with a 1-year remission.

Video electroencephalography when the patient relapsed at age 5 years showed focal slowing present intermittently over both hemispheres, multifocal epileptiform discharges, and frequent clinical and subclinical seizures from the right occipital electrodes. Repeat magnetic resonance imaging at ages 5 and 6 years (Fig 4) revealed progressive volume loss, fluid-attenuated inversion recovery changes, and new areas of cortical thinning. Neuropsychiatric testing showed full-scale IQ of 79, with a significant difference between verbal (78) and performance IQ (94) scores. Clinically, there was a significant deterioration in the patient's school performance.

Lumbar puncture showed cerebrospinal fluid glucose of 36 and concurrent plasma glucose of 101, five oligoclonal bands, and normal lactate, pyruvate, and neurotransmitters. A paraneoplastic panel was positive for striational acetylcholine receptor antibody 1:120. Chromosome microarray, mitochondrial sequencing and epilepsy panel were negative. Systemic markers of inflammation and thyroid studies were negative. Whole body imaging for tumor was negative. Seizures remained refractory despite oxcarbazepine, topiramate, and clobazam.

Intravenous immunoglobulin 1 g/kg monthly was initiated with remission of the seizures. Repeat magnetic resonance imaging at 6 months, 1 year, and 18 months into the intravenous immunoglobulin treatment showed no further progression of volume loss. Repeat lumbar puncture 8 months after initiation of intravenous immunoglobulin showed cerebrospinal fluid glucose 44 and concurrent plasma glucose of 80, more than five oligoclonal bands, and normal lactate and pyruvate