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Clinical Observations

The Fault in Their Stars—Accumulating Astrocytic Inclusions Associated With Clusters of Epileptic Spasms in Children With Global Developmental Delay

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ABSTRACT

BACKGROUND: The presence of cerebral astrocytic inclusions recently has been described in a subset of children with early-onset refractory epilepsy, with or without structural brain malformations, and varying degrees of developmental delay. **METHODS:** We describe two new individuals with epilepsy with astrocytic inclusions and suggest that in some children this disorder may represent a unique hemispheric epilepsy. We review previously reported individuals with epilepsy with astrocytic inclusions. **RESULTS:** Two children with early onset epilepsy with astrocytic inclusions had refractory clusters of epileptic spasms, developmental delay, abnormal neuroimaging, and hemispheric or diffuse interictal epileptiform discharges. In both children, the initial focal resection of the putative epileptogenic zone was unsuccessful and pathology failed to show astrocytic inclusions. Subsequently, both children underwent functional hemispherectomy due to ongoing clusters of epileptic spasms, and the presence of multilobar astrocytic inclusions was demonstrated. Postoperatively, both children have remained seizure free in the short-term with improved development. **CONCLUSIONS:** We highlight that functional hemispherectomy may be required for seizure control in a select subset of children with clusters of epileptic spasms, astrocytic inclusions, and global developmental delay. Given the small number of documented patients, however, ongoing collaboration is needed to better understand the pathophysiology of this condition and determine the optimal way to diagnose and manage these children.

Keywords: filaminopathy, astrocytic inclusions, hemispherectomy, epileptic spasms, childhood epilepsy

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Introduction

Recently there has been increasing interest in a subset of children with early-onset medically refractory epilepsy, with or without structural brain malformations and developmental delay, whose pathology shows the presence of astrocytic inclusions (AIs).[1-10] AIs are found exclusively within the cortex and may extend to areas outside cortical malformations.[2,4,5] The term "filaminopathy" has been used to describe these unique findings, given the presence of filamin A within the AIs.[1,2,4-6] Filamin A is a protein involved in actin cross-linking which plays an important role in neuronal migration.[1,2,11] Dysfunction of the filamin pathway may be implicated in the development of AIs.[2] Interestingly, similar inclusions have been described in Aicardi syndrome.[11,12]

Despite the presence of AIs, it remains speculative whether the inclusions play a role in the development of seizures or occur as a result of them. The lack of seizure freedom after focal cortical resection[1,2,8] as well as hemispheric or generalized abnormalities on the electroencephalograph (EEG)[1] may suggest a more extensive

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epileptogenic network in medically refractory epilepsy due to filaminopathy. The objective of this article is to demonstrate that: (1) epilepsy with AIs may manifest as a diffuse hemispheric disease, in which the AIs may possibly contribute to ongoing clusters of epileptic spasms and (2) focal cortical resection is sometimes unsuccessful in epilepsy with AIs, and functional hemispherectomy may be required for seizure control in a subset of children with clusters of epileptic spasms and global developmental delay.

Methods

Clinical data

Consent was obtained from both patients' families in accordance with the research ethics board at the Hospital for Sick Children. A comprehensive review was undertaken of the patients' medical histories, diagnostic imaging, EEG, and pathology findings.

Results

Patient 1

This is a 2.5-year-old boy with an unremarkable birth and pregnancy history, global developmental delay, and seizure onset at 3.5 months (Table). Initial seizures consisted of daily clusters of epileptic spasms without lateralizing signs and focal seizures with eye deviation upward, head deviation to the right, and tonic stiffening of the limbs. The seizures were refractory to several antiepileptic drugs.

EEG at seizure onset revealed intermittent spike waves and slowing over the left frontal central head regions. One month later, EEG showed left-sided hemihypsarrhythmia. Magnetic resonance imaging (MRI) of the brain at four months demonstrated extensive left frontal polymicrogyria (PMG) (Fig 1).

At five months of age, he underwent left frontal lobectomy with removal of the PMG. Pathology confirmed the presence of left frontal PMG. Nine months later, the focal seizures and clusters of epileptic spasms recurred. Developmentally, he could partially roll and hold his head, occasionally smile, and was nonverbal. Examination showed left hand preference and increased tone and deep tendon reflexes on the right.

At 20 months, prolonged video EEG was performed. Ictally the clusters of epileptic spasms were associated with diffuse high-amplitude delta waves followed by attenuation; the focal seizures had a nonlateralizing onset. The spasms preceded the focal seizures approximately 70% of the time. Interictally, there were frequent left central-

TABLE.
Summary of Clinical Course, EEG, Neuroimaging, and Pathology Findings

	Patient 1	Patient 2
Age/sex	2 years, 6 months Male	3 years, 11 months Female
Age of seizure onset	3.5 months	5 months
Type of seizures	Focal/clusters of epileptic spasms	Focal/clusters of epileptic spasms
Development at seizure onset	Global delay	Normal
Current development	Profound global delay Laughs, smiles, nonverbal, partially rolling, sits with support	Moderate global delay Receptive language at 24 months, visual fine motor 17 months, and expressive language 12 months
MRI	Extensive left frontal polymicrogyria with reduced white matter	Increased T2 signal noted diffusely in the white matter of the right frontal lobe
First surgery age (months)	5 months	17 months
Type	Left frontal lobectomy	Right frontal lobectomy
Pathology	Polymicrogyria	Gliosis
Seizure recurrence after first surgery	9 months	5 months
EEG		
Initial EEG	Left frontal-central IEDs and slowing over this region	Right frontal IEDs
EEG before hemispherectomy	Diffuse left hemispheric IEDs Poor sleep features on left Diffuse and nonlateralizing ictal onset	Diffuse right hemispheric IEDs Poor sleep features on right Right hemispheric ictal onset
Age at hemispherectomy (years, months)	2 years	3 years 7 months
Interval between seizure onset and hemispherectomy (months)	21 months	38 months
Repeat pathology	Astrocytic inclusions: left occipital pole, left mesial occipital lobe, left temporal lobe, and pole	Astrocytic inclusions: right parietal, right temporal lobe, right temporal pole, right inferior/posterior temporal lobe, and residual right frontal lobe
Current status	Seizure free for 6 months Improved head control Level of engagement improved	Seizure free for 4 months Right-sided hemiparesis Improved expressive language Level of engagement improved

Abbreviations:
EEG = Electroencephalograph
IEDs = Interictal epileptiform discharges
MRI = Magnetic resonance imaging