

# Child Neurology: Pediatric seizures with hyaline astrocytic inclusions

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Astrocytic dysfunction is implicated in epilepsy through many proposed molecular mechanisms, but there is also a clinicopathologic entity of epilepsy featuring astrocytic inclusions.<sup>1</sup> At least 17 cases of early-onset epilepsy with eosinophilic, hyaline astrocytic inclusions have been reported since the early 1990s.<sup>2-8</sup> Most of these cases also involve developmental delay.<sup>2-8</sup> The diagnosis is made by neuropathologic analysis that demonstrates brightly eosinophilic, hyaline, refractile astrocytic inclusions seen under light microscopy with hematoxylin & eosin stain.<sup>2-8</sup> We review the clinicopathologic entity of pediatric epilepsy with hyaline astrocytic inclusions and report an illustrative case.

**Clinical history.** A 6-year-old boy first developed seizures and developmental delay at 4 months of age. Until then, his medical history had been unremarkable. His seizures initially consisted of staring spells and generalized shaking, which progressed to infantile spasms that were controlled with adrenocorticotropic hormone. He was seizure-free for a year, and then developed atonic seizures that responded well to levetiracetam. EEG at age 5 months showed bihemispheric disturbance consistent with a generalized epileptiform process. EEG at age 2.5 years showed mild slowing of background rhythms, worse on left than right, with some sharp wave discharges from the left frontal region, consistent with mild encephalopathy and a focal source of seizures. At age 4 years, during a 14-month seizure-free period, 24-hour EEG was within normal limits. MRI brain was initially interpreted as showing mild corpus callosal body thinning, but upon later review, an abnormally deep gyrus with thickened gray matter was identified in the right frontal lobe. At age 5.5 years, he developed new seizures characterized by left-sided weakness after atonic seizures and cyclical vomiting. MRI was unchanged (figure, A). His seizures increased in frequency in the next few months, so he was started on rufinamide.

At age 6, he continued to have seizures that occurred every 3-5 days. He had atonic seizures with backward falls, as well as complex partial seizures with

altered awareness, slow eye blinking, lip smacking, drooling, and left-sided weakness. Some seizures were associated with teeth grinding or emesis. Seizures usually lasted less than 5 minutes. Developmentally, he was largely nonverbal, but could make letter sounds and some signs. He could follow simple one-step commands with repetition and reinforcement from his parents. He could not read or write, but could do some drawing and counting. He required aid for dressing, but could use utensils. His gross motor skills were largely intact. He exhibited some self-stimulatory behavior, including increased hand biting. He was eventually also diagnosed with autism.

On examination at age 6, he appeared anxious and crying, but was alert. He was biting his hands, and had bite marks on both hands and wrists. He followed some commands, and communicated largely with grunts and gestures. The rest of the physical and neurologic examination was unremarkable. Epilepsy monitoring unit revealed interictal epileptiform activity maximal in the right frontotemporal region, seizure onset in the same area, and diffuse encephalopathy. Interictal SPECT showed reduction in perfusion of anteromesial frontal lobes bilaterally. Ictal SPECT could not be obtained. PET showed hypometabolism in the posterior and inferior right frontal lobe (figure, B).

Family history was positive for Asperger syndrome in a first cousin. Genetic testing was negative for abnormalities in male chromosomes, *ARX*, *MED12*, X-linked mental retardation panel, Rett-like syndrome, and neuroligin genes. A 180K microarray was normal. Thyroid studies were normal.

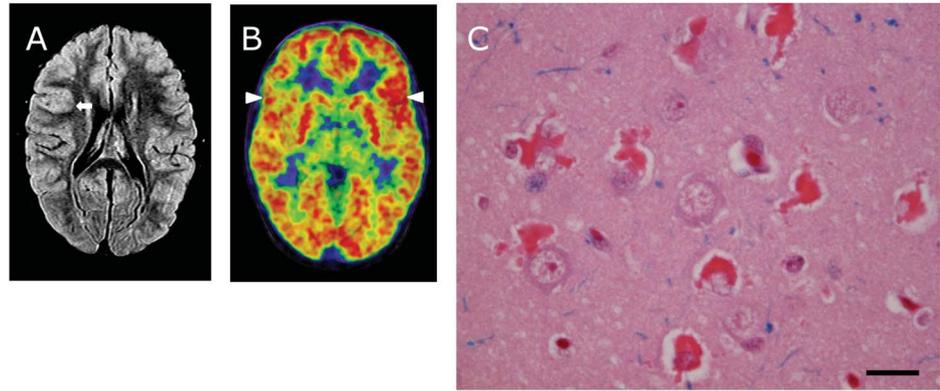
At age 6, he underwent right craniotomy for implantation of extensive right frontal and temporal subdural electrode arrays. He then underwent a wide surgical resection of the frontal lobe ictal onset zone encompassing preoperative imaging abnormalities. He has remained seizure-free for 3 months since surgical resection.

**Neuropathologic analysis.** Sections of the most active area of seizures, deeper areas, posterior frontal lobe,

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**Figure** Brain imaging and neuropathologic analysis of one boy with pediatric epilepsy with hyaline astrocytic inclusions



(A) Fluid-attenuated inversion recovery MRI brain at age 5 shows an abnormally deep sulcus in the right frontal lobe with thickened gray matter (arrow). (B) Preoperative PET brain scan at age 6 shows decreased metabolism in the right frontal lobe compared to the left (arrowheads). (C) Under light microscopy, hematoxylin & eosin stain of surgically resected brain tissue from the middle frontal lobe reveals brightly eosinophilic, hyaline, refractile inclusions in cortical astrocytes (bar length represents 30  $\mu\text{m}$ ).

and middle frontal lobe were analyzed. Histopathologic analysis showed accumulation of eosinophilic, hyaline, refractile, filamin-positive astrocytic inclusions extending through all cortical layers, but not in white matter (figure, C). There was a predilection for more superficial cortical layers in lesser-affected areas. All sections had these inclusions. Inclusions were not increased in cortical areas disrupted by preoperative seizure monitoring procedures. They were not associated with inflammation, neuronal loss, or major neuronal dysmorphism. There were no giant, immature, or dysmorphic neurons. There was mild Chaslin subpial gliosis. There were no pachygyria, heterotopias, or major gyral abnormalities. There was a suggestion of horizontal cortical dyslamination, but no vertical columnar disorientation.

**DISCUSSION** This case illustrates pediatric epilepsy with eosinophilic, hyaline astrocytic inclusions, a disease affecting both male and female patients.<sup>2-8</sup> Key clinical characteristics of pediatric epilepsy with hyaline astrocytic inclusions are developmental delay and seizures. Developmental delay does not seem to have a predilection for specific domains and is usually severe.<sup>5,6</sup> In at least 2 cases, however, developmental delay is absent.<sup>2,3</sup> It is unclear from many of the case reports whether developmental delay worsens or begins with seizure onset, as in our case and at least one other case.<sup>6</sup> Seizures may begin to occur from 2 months to 2 years, and can be partial or generalized.<sup>2-8</sup> Seizures are often intractable despite treatment with antiepileptic drugs.<sup>2-8</sup> Of 12 patients who underwent surgical resection of epileptic foci,<sup>2,3,5-7</sup> 3 patients had recurrent seizures with reduced frequency,<sup>2,6</sup> and 4 remained seizure-free for various periods of time by time of

publication.<sup>2,3,6</sup> One patient died shortly after surgical resection complicated by a vascular event.<sup>6</sup> Clinical outcomes after surgical resection of epileptic foci were not reported in 4 patients.<sup>5,7</sup>

Brain malformations are present in some<sup>4-6,8</sup> but not all cases of pediatric epilepsy with hyaline astrocytic inclusions.<sup>3,5,7</sup> Malformations present include cortical dysplasia,<sup>6</sup> polymicrogyria,<sup>4,5,8</sup> periventricular heterotopias,<sup>4-6,8</sup> periventricular white matter changes,<sup>6</sup> pachygyria,<sup>8</sup> cerebellar vermis hypoplasia,<sup>8</sup> or agenesis of corpus callosum.<sup>6,8</sup> Non-CNS congenital abnormalities are sometimes reported, and include cardiac septal defect, bowel malrotation, and upper extremity deformity.<sup>6</sup>

In pediatric seizures with hyaline inclusions, these inclusions are found throughout the cerebral cortex and are absent from white matter, cerebellum, brainstem, or subcortical gray matter, but are not restricted to regions of brain malformations.<sup>4-6</sup> These inclusions commonly appear semi-lunar in morphology.<sup>4-6</sup> Seen under electron microscopy, astrocytic inclusions appear granular and osmiophilic.<sup>2,4,5</sup> Astrocytes with these inclusions can be hypertrophic.<sup>3,4</sup> These eosinophilic astrocytic inclusions are different from other types of eosinophilic astrocytic inclusions, such as Rosenthal fibers found in Alexander disease and other conditions<sup>9</sup>; unlike Rosenthal fibers, these inclusions appear nonfilamentous, stain negative for ubiquitin and glial fibrillary acidic protein, reside in protoplasmic instead of fibrous astrocytes, and spare subpial and perivascular areas.<sup>3-6</sup> Aicardi syndrome has similar eosinophilic astrocytic inclusions, but affects only female patients, featuring the triad of corpus callosal agenesis, retinal lacunae, and infantile spasms.<sup>10</sup>

The functional significance of hyaline astrocytic inclusions in epilepsy or developmental delay remains unknown, but is a topic of research interest. These inclusions stain variably for proteins but are resistant to RNAse digestion,<sup>3</sup> so pediatric epilepsy with hyaline astrocytic inclusions can be considered a proteinopathy.<sup>5</sup> In our case and others, these inclusions are positive for filamin A, which is also positive in astrocytic inclusions in X-linked dominant Aicardi syndrome, leading to speculation that pediatric epilepsy with hyaline astrocytic inclusions lies on a spectrum with Aicardi syndrome.<sup>2,5,6</sup> Astrocytic inclusions are also variably positive for S-100 protein,<sup>2,3,8</sup> heme-oxygenase 2,<sup>5</sup> cytoglobin,<sup>2,5</sup> GLT1,<sup>5</sup> and  $\alpha$ -B-crystallin,<sup>2</sup> and negative for ubiquitin,  $\alpha$ -synuclein,  $\beta$ -amyloid, heat shock proteins 27 and 70, and tau.<sup>3</sup> Inclusions are positive in one study<sup>2</sup> but negative in another study for glial fibrillary acidic protein.<sup>3</sup> A recent proteomics study reports increased levels of catalase and carbonic anhydrase I in resected epileptic brain tissue.<sup>7</sup>

Pediatric epilepsy with hyaline astrocytic inclusions should be included on the differential diagnosis for seizures with developmental delay, especially but not exclusively with brain malformations. Some clinical features that raise suspicion of pediatric epilepsy with hyaline astrocytic inclusions include EEGs with both generalized abnormalities and focal sources of seizures, intractable seizures despite antiepileptic drugs, and MRI with subtle to major structural abnormalities. Although this proteinopathy likely affects widespread areas of the brain, the majority of patients with pediatric epilepsy with hyaline astrocytic inclusions who underwent surgical resection of epileptic foci had some improvement in seizures, so this disease entity has potentially effective and feasible interventions.<sup>2,3,6</sup> On a fundamental level, the protein inclusions in this disease entity may yield more clues about the relationship between astrocytic dysfunction and the mechanisms underlying epilepsy and developmental delay. This disease is one of the few seizure conditions in which the abnormality lies in astrocytes instead of neurons, emphasizing the importance of glial cells in neuronal disease.

## AUTHOR CONTRIBUTIONS

Janice C. Wong: writing of manuscript, literature review, project design. Brent O'Neill: clinical evaluation and care of patient, manuscript review. Cynthia E. Hawkins: manuscript review, project design. B.K. Kleinschmidt-DeMasters: provided case, manuscript review, project design. Lili-Naz Hazrati: manuscript review, project design.

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