Child Neurology:
Pediatric seizures with hyaline astrocytic inclusions

Astrocytic dysfunction is implicated in epilepsy through many proposed molecular mechanisms, but there is also a clinicopathologic entity of epilepsy featuring astrocytic inclusions.1 At least 17 cases of early-onset epilepsy with cosinophilic, hyaline astrocytic inclusions have been reported since the early 1990s.2–8 Most of these cases also involve developmental delay.2–8 The diagnosis is made by neuropathologic analysis that demonstrates brightly cosinophilic, hyaline, refractile astrocytic inclusions seen under light microscopy with hematoxylin & eosin stain.2–8 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 normal. Thyroid studies were normal. X-linked mental retardation panel, Rett-like syndrome, and neuriligin 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,
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. 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. In at least 2 cases, however, developmental delay is absent. 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. Seizures may begin to occur from 2 months to 2 years, and can be partial or generalized. Seizures are often intractable despite treatment with antiepileptic drugs. Of 12 patients who underwent surgical resection of epileptic foci, 3 patients had recurrent seizures with reduced frequency, and 4 remained seizure-free for various periods of time by time of publication. One patient died shortly after surgical resection complicated by a vascular event. Clinical outcomes after surgical resection of epileptic foci were not reported in 4 patients.

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

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. These inclusions commonly appear semi-lunar in morphology. Seen under electron microscopy, astrocytic inclusions appear granular and osmiophilic. Astrocytes with these inclusions can be hypertrophic. These eosinophilic astrocytic inclusions are different from other types of eosinophilic astrocytic inclusions, such as Rosenthal fibers found in Alexander disease and other conditions; 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. Aicardi syndrome has similar eosinophilic astrocytic inclusions, but affects only female patients, featuring the triad of corpus callosal agenesis, retinal lacunae, and infantile spasms.

(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 μm).
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, so pediatric epilepsy with hyaline astrocytic inclusions can be considered a proteinopathy. 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. Astrocytic inclusions are also variably positive for S-100 protein, heme-oxygenase 2, cytoglobin, GLT1, and α-B-crystallin, and negative for ubiquitin, α-synuclein, β-amyloid, heat shock proteins 27 and 70, and tau. Inclusions are positive in one study but negative in another for glial fibrillary acidic protein. A recent proteomics study reports increased levels of catalase and carbonic anhydrase I in resected epileptic brain tissue.

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. 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.

**REFERENCES**


Child Neurology: Pediatric seizures with hyaline astrocytic inclusions
Janice C. Wong, Brent O'Neill, Cynthia E. Hawkins, et al.
*Neurology* 2013;81:e14-e16
DOI 10.1212/WNL.0b013e31829bfe54

This information is current as of July 15, 2013

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://www.neurology.org/content/81/3/e14.full.html">http://www.neurology.org/content/81/3/e14.full.html</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 10 articles, 4 of which you can access for free at: <a href="http://www.neurology.org/content/81/3/e14.full.html##ref-list-1">http://www.neurology.org/content/81/3/e14.full.html##ref-list-1</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): All Epilepsy/Seizures <a href="http://www.neurology.org/cgi/collection/all_epilepsy_seizures">http://www.neurology.org/cgi/collection/all_epilepsy_seizures</a> All Pediatric <a href="http://www.neurology.org/cgi/collection/all_pediatric">http://www.neurology.org/cgi/collection/all_pediatric</a> Developmental disorders <a href="http://www.neurology.org/cgi/collection/developmental_disorders">http://www.neurology.org/cgi/collection/developmental_disorders</a> Epilepsy surgery <a href="http://www.neurology.org/cgi/collection/epilepsy_surgery">http://www.neurology.org/cgi/collection/epilepsy_surgery</a>_</td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/misc/about.xhtml#permissions">http://www.neurology.org/misc/about.xhtml#permissions</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://www.neurology.org/misc/addir.xhtml#reprintsus">http://www.neurology.org/misc/addir.xhtml#reprintsus</a></td>
</tr>
</tbody>
</table>