


Brain Inflammation in an Infant With Hemimegalencephaly, Escalating Seizures, and Epileptic Encephalopathy

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Abstract

Hemimegalencephaly, a congenital brain malformation typically characterized by enlargement of one hemisphere, is frequently associated with intractable epilepsy. The authors report a case of a 12-month-old girl with hemimegalencephaly who underwent semiurgent hemispherectomy because of rapidly escalating seizures, arrested development, and associated encephalopathy. The brain tissue was examined and evaluated for neuroinflammation. Immunohistochemical analysis of the brain tissue revealed the presence of abundant activated CD68-positive microglia and reactive astrogliosis. Detection of active inflammatory changes in the brain of a patient with hemimegalencephaly complicated by intractable epilepsy suggests a potential role of ongoing brain inflammation in seizure exacerbation and epileptic encephalopathy.

Keywords

early-onset seizures, epilepsy, malformations of cortical development, hemispherectomy, neuroinflammation

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Hemimegalencephaly is a congenital brain malformation that is typically characterized by enlargement of one hemisphere of the brain and is associated with abnormal migration and proliferation of neurons and glial cells. Histological findings include large abnormal neurons, neuronal cytomegaly, and giant astrocytes.¹ Seizures appear within the first 6 months of life and are frequently refractory to medical therapy. Epilepsy surgery is usually necessary for the control of seizures.²

The underlying mechanism for epileptogenicity and progression of seizures in patients with hemimegalencephaly remains unknown. The immaturity and dysfunction of neurons have been suggested as the probable underlying cause of the intractable epilepsy.³ However, this does not fully explain the frequently observed finding of exacerbation of seizures in these patients.

Recent studies have suggested an important role of inflammation in generating and exacerbating epilepsy.^{4,5} In experimental animals, complement activation in cerebral cortex or intraventricular infusion of proinflammatory cytokines provoked and exacerbated seizures,^{6,7} while induced systemic inflammation increased seizure susceptibility.^{8,9} In patients with hippocampal sclerosis and frequent seizures, inflammatory changes in

the temporal lobe were observed.¹⁰ Here, the authors speculated that inflammation can play a role in the worsening of seizures and mental status in a patient with hemimegalencephaly. The authors found activated microglia and reactive astrogliosis in a brain of 12-month-old girl with hemimegalencephaly in whom seizures increased in frequency and severity and showed developmental regression. She became seizure free after hemispherectomy.

Case Summary

A 2-month-old girl had a single unprovoked seizure characterized by bilateral eye fluttering and symmetric limb jerking over

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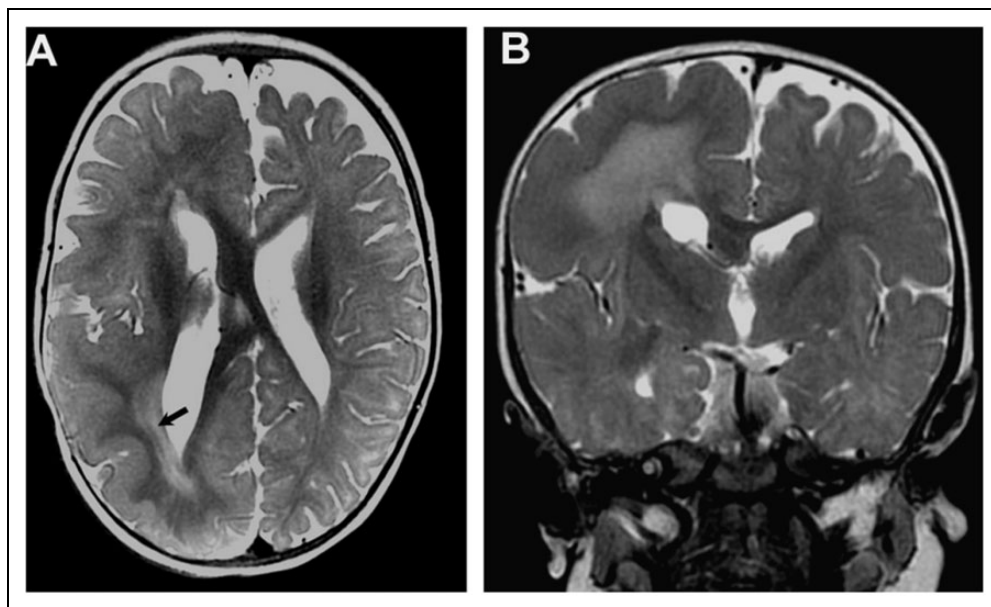


Figure 1. Axial (A) and coronal (B) T2-weighted brain magnetic resonance image at 8 months old showed diffuse enlargement of the right hemisphere with diffusely thickened right frontal and temporal lobes. Mild hyperintense signal was noted in the subcortical white matter. In the right parietal-occipital lobe, periventricular white matter with a striated appearance was noted (arrow), which suggested band heterotopia.

10 seconds. This went unrecognized as a seizure by her parents until it recurred at 5 months of age for 20 seconds. History was remarkable for a normal term delivery and “crossed eyes” since birth. Neonatal course and early development were normal. Family history did not reveal any neurological disease. Initial examination at 5 months was normal, but interictal electroencephalography showed focal epileptiform discharges on the right frontal central area and focal monomorphic theta on the right frontal area. The third seizure occurred at age 7 months and was characterized by drooling, mild cyanosis, bilateral eye fluttering (left greater than right), and left hemiconvulsion. Magnetic resonance imaging of the brain showed enlargement of the majority of the right cerebral hemisphere, with associated diffuse cortical thickening and white matter signal abnormality and right lateral ventricular enlargement (Figure 1). Despite initiation and titration of topiramate, the frequency of short focal seizures increased to 10 per day. Carbamazepine was added as the seizure frequency continued to increase up to 20 per day. By 10 months of age, seizures remained refractory to trials of fosphenytoin, carbamazepine, topiramate, levetiracetam, and phenobarbital. Examination was remarkable for intermittent loss of alertness and visual attentiveness, right gaze preference, left hemiparesis affecting the arm greater than the leg, and generalized hypotonia. Electroencephalography showed nearly continuous epileptiform activity and precocious fast rhythms from the right hemisphere. Right hemispherectomy was performed at age 12 months and she had no further seizures for 5 years from the day of surgery. Anticonvulsants were weaned off after 2 years’ seizure free. At 6 years of age, she was a talkative young girl with outgoing personality and a limited use of her left hand with a weak grasp. She could run well and learned to ride a tricycle.

Methods

Brain Tissue Processing

Resected brain tissue was obtained from the operating room with parental consent. Sections were cut into 5-mm³ slices and emersion fixed. Basic histological examination was performed after hematoxylin–eosin staining. The tissue was processed for immunohistochemistry as described previously.^{10,11} Antibodies to glial fibrillary acidic protein (GFAP; 1:100, DAKO, Glostrup, Denmark) were used to visualize astrocytes, neuronal nuclear protein (NeuN, Chemicon, Temecula, California) for neurons, and CD 68 (KP1, 1:100, DAKO) for microglia/macrophage.

Results

Microscopically, sections showed disorganization of the normal cortical laminar architecture with scattered giant, dysmorphic neurons, and subcortical aggregates of neurons in the white matter. Immunostaining for glial fibrillary acidic protein showed subpial gliosis and cortical astrogliosis especially around the cerebral blood vessels (Figure 2A). Immunolabeling of CD68 revealed a large number of activated microglia involving both cortex and white matter of the resected tissue diffusely (Figure 2B).

Discussion

This case illustrates the presence of inflammation in the brain tissue of a patient with intractable epilepsy due to hemimegalencephaly and supports the findings of prior studies showing a close association between epilepsy and neuroinflammation.^{11–13} The clinical pattern of single isolated seizures progressing to daily seizures is common with severe malformations of cortical development, such as hemimegalencephaly. Long-term effects

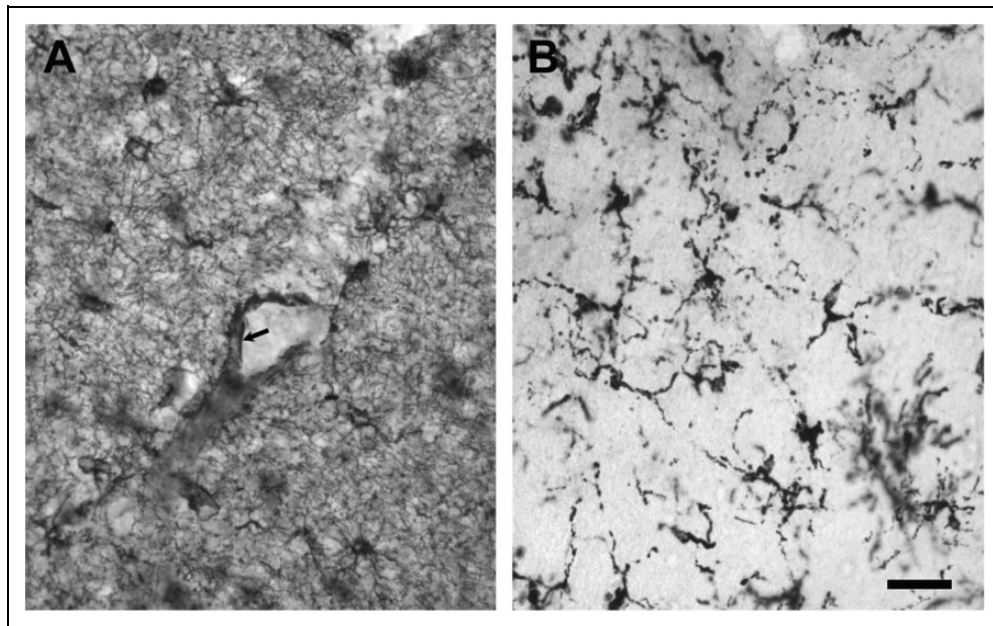


Figure 2. A, Immunohistochemistry with antiglial fibrillary acidic protein (GFAP) antibody. Cortex and white matter are covered by markedly increased astrocytes with profuse astrocytic processes, especially around the cerebral blood vessels (arrow). B, Immunohistochemical analysis using anti-CD68 antibody in temporal lobe. CD-68 immunoreactive, activated microglia is distributed diffusely in the cortex and white matter. Scale bar = 25 μ m.

of recurrent seizures in this condition include progressive calcification and atrophy related to chronic inflammation.¹⁴ The duration of epilepsy and the frequency of seizures are both implicated in this process.¹³

Animal studies demonstrate that seizures early in life increase the risk of subsequent seizures.¹⁵ Further experiments determined that the seizures caused long-term glial activation and increased susceptibility to seizures. An inhibitor of cytokine production and microglia activation were shown to prevent neuroinflammation and block subsequent increase in seizure susceptibility.^{16,17} Despite these data in rodent models, it remains difficult to prove the epileptogenic effect of recurrent seizures and inflammation in humans. Here the authors show escalating seizures, and encephalopathy are accompanied by glial activation in the patient's brain.

A prospective clinical study examined the length of time before epilepsy became intractable in a group of children.¹⁸ Focal structural epilepsy often followed a pattern of temporary seizure remissions that delayed reaching intractable status, therefore, undue delay in referral for surgery. Yet, complete resolution of childhood epilepsy is highly unlikely in the presence of a brain lesion.¹⁹ Within one year, the resected brain tissue from our patient showed widespread gliosis, marked activation of both microglia and astrocytes, consistent with early changes of eventual calcification and atrophy.¹⁴ Our finding supports the role of active brain inflammation to predispose, precipitate, and perpetuate epileptogenic encephalopathy.

Immunomodulatory therapy may be indicated in very young infants with a structural lesion and intractable epilepsy for whom surgery needs to be delayed due to concern for intraoperative mortality and morbidity associated with excess blood loss. The

youngest hemispherectomy case for hemimegalencephaly reported in the literature is 7 weeks of age.²⁰ It is, indeed, rare to perform functional hemispherectomy in young infants prior to 12 months of age or about 10 kg weight.²¹ In Rasmussen encephalitis, a prototypical immune inflammatory epilepsy, greater than 50% seizure reduction was achieved by monthly steroid pulse therapy (81%) that compared favorably to tacrolimus (42%) or to intravenous immunoglobulin (IVIG) therapy (23%).²² Seizure freedom was afforded by hemispherectomy up to 71% of patients, while only 8% by tacrolimus and 5% by pulse steroid and none by IVIG. By initiating steroid pulse therapy early, functional hemispherectomy may be prevented or delayed and hemiparesis, avoided.²² Given the evidence for chronic inflammation in our patient with hemimegalencephaly, there may be a window of opportunity to initiate immunomodulatory therapies in nonsurgical cases or in cases where hemispherectomy is unavoidably delayed. Immunomodulation can prevent neuroinflammation, epileptic encephalopathy, and evolution to catastrophic intractable epilepsy.

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Author Contributions

SHK and JJM were equally responsible for the first draft of the manuscript. JJM was responsible for clinical care of the patient. SHK performed immunohistochemistry. SK was responsible for the overall conduct of the study and obtained institutional review board approval and brain tissue.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was approved by the institutional review board of the Ann & Robert H. Lurie Children's Hospital of Chicago.

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