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

Se Hee Kim, Northwestern University  
John J. Millichap, Northwestern University  
Sookyong Koh, Emory University

Journal Title: Child Neurology Open  
Volume: Volume 3, Number 0  
Publisher: SAGE Publications (UK and US) | 2016-04-04  
Type of Work: Article | Final Publisher PDF  
Publisher DOI: 10.1177/2329048X16633629  
Permanent URL: https://pid.emory.edu/ark:/25593/s2r89

Final published version: http://dx.doi.org/10.1177/2329048X16633629

Copyright information:

© 2016 The Author(s)

This is an Open Access work distributed under the terms of the Creative Commons Attribution-Noncommercial 3.0 Unported License (http://creativecommons.org/licenses/by-nc/3.0/).

Accessed November 12, 2023 10:10 AM EST
Brain Inflammation in an Infant With Hemimegalencephaly, Escalating Seizures, and Epileptic Encephalopathy

Se Hee Kim, MD¹, John J. Millichap, MD¹, and Sookyong Koh, MD, PhD²

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 semieurgent 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

Received December 3, 2015. Received revised January 19, 2016. Accepted for publication January 23, 2016.

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 for...
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. 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 laminal architecture with scattered giant, dysmorphic neurons, and subcortical aggregates of neurons in the white matter. Immunostaining for glial fibrillary acidic protein (GFAP, 1:100, DAKO, Glostrup, Denmark) was used to visualize astrocytes, neuronal nuclear protein (NeuN, Chemicon, Temecula, California) for neurons, and CD 68 (KP1, 1:100, DAKO) for microglia/macrophage. 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. 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.

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

Animal studies demonstrate that seizures early in life increase the risk of subsequent seizures. 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. 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. 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. 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. 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. It is, indeed, rare to perform functional hemispherectomy in young infants prior to 12 months of age or about 10 kg weight. 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%). 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. 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.

Acknowledgments
This work was completed at Ann & Robert H. Lurie Children’s Hospital of Chicago, the pediatric teaching hospital for Northwestern University Feinberg School of Medicine.

Author Contributions
SHK and J JM were equally responsible for the first draft of the manuscript. J JM 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.

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 μm.
Declaration of Conflicting Interests

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

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by NIH/NINDS R01 NS073768 (SK).

Ethical Approval

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

References

1. Flores-Sarnat L, Sarnat HB, Davila-Gutierrez G, Alvarez A. Hemimegalencephaly: part 2. Neuropathology suggests a disorder of cellular lineage. J Child Neurol. 2003;18(11):776-785.
2. Bulteau C, Otsuki T, Delalande O. Epilepsy surgery for hemispheric syndromes in infants: Hemimegalencephaly and hemispheric cortical dysplasia. Brain Dev. 2013;35(8):742-747.
3. Ariai A, Saito T, Hanai S, et al. Abnormal maturation and differentiation of neocortical neurons in epileptogenic cortical malformation: unique distribution of layer-specific marker cells of focal cortical dysplasia and hemimegalencephaly. Brain Res. 2012;1470:89-97.
4. Xu D, Miller SD, Koh S. Immune mechanisms in epileptogenesis. Front Cell Neurosci. 2013;7:195.
5. Vezzani A, French J, Bartfai T, Baram TZ. The role of inflammation in epilepsy. Nat Rev Neurol. 2011;7(1):31-40.
6. Dube C, Vezzani A, Behrens M, Bartfai T, Baram TZ. Interleukin-1beta contributes to the generation of experimental febrile seizures. Ann Neurol. 2005;57(1):152-155.
7. Xiong ZQ, Qian W, Suzuki K, McNamara JO. Formation of complement membrane attack complex in mammalian cerebral cortex evokes seizures and neurodegeneration. J Neurosci. 2003;23(3):955-960.
8. Eun BL, Abraham J, Mlsna L, Kim MJ, Koh S. Lipopolysaccharide potentiates hyperthermia-induced seizures. Brain Behav. 2015;14(5):600348.
9. Sayyah M, Javad-Pour M, Ghazi-Khansari M. The bacterial endotoxin lipopolysaccharide enhances seizure susceptibility in mice: involvement of proinflammatory factors: nitric oxide and prostaglandins. Neuroscience. 2003;122(4):1073-1080.
10. Crespel A, Coubes P, Rouset MC, et al. Inflammatory reactions in human medial temporal lobe epilepsy with hippocampal sclerosis. Brain Res. 2002;952(2):159-169.
11. Choi J, Nordli DR Jr, Alden TD, et al. Cellular injury and neuroinflammation in children with chronic intractable epilepsy. J Neuroinflammation. 2009;6:38.
12. Ravizza T, Gagliardi B, Noe F, Boer K, Aronica E, Vezzani A. Innate and adaptive immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy. Neurobiol Dis. 2008;29(1):142-160.
13. Boer K, Spliet WG, van Rijen PC, Redeker S, Troost D, Aronica E. Evidence of activated microglia in focal cortical dysplasia. J Neuroimmunol. 2006;173(1-2):188-195.
14. Nonoda Y, Saito Y, Itoh M, et al. Activation of microglia/macrophages expressing phosphorylated S6 ribosomal protein in a case of hemimegalencephaly with progressive calcification and atrophy. J Neurol Sci. 2009;287(1-2):52-59.
15. Koh S, Storey TW, Santos TC, Mian AY, Cole AJ. Early-life seizures in rats increase susceptibility to seizure-induced brain injury in adulthood. Neurology. 1999;53(5):915-921.
16. Abraham J, Fox PD, Condello C, Bartolini A, Koh S. Minocycline attenuates microglia activation and blocks the long-term epileptogenic effects of early-life seizures. Neurobiol Dis. 2012;46(2):425-430.
17. Somera-Molina KC, Robin B, Somera CA, et al. Glial activation links early-life seizures and long-term neurologic dysfunction: evidence using a small molecule inhibitor of proinflammatory cytokine upregulation. Epilepsia. 2007;48(9):1785-1800.
18. Berg AT, Vickrey BG, Testa FM, et al. How long does it take for epilepsy to become intractable? A prospective investigation. Ann Neurol. 2006;60(1):73-79.
19. Berg AT, Rychlik K, Levy SR, Testa FM. Complete remission of childhood-onset epilepsy: stability and prediction over two decades. Brain. 2014;137(pt 12):3213-3222.
20. Cuddapah VA, Thompson M, Blount J, Li R, Gueresta S, Goyal M. Hemispherectomy for Hemimegalencephaly Due to Tuberculous Sclerosis and a Review of the Literature. Pediatr Neurol. 2015;53(5):452-455.
21. Nachanakian A, Hmimess G, El-Helou A, Alaywan M, Adem-Hachem C, Kadhim H. Early modified functional hemispherectomy in a young infant with Ohtahara syndrome and hemimegalencephaly. J Child Neurol. 2015;30(4):522-526.
22. Takahashi Y, Yamazaki E, Mine J, et al. Immunomodulatory therapy versus surgery for Rasmussen syndrome in early childhood. Brain Dev. 2013;35(8):778-785.