BIOGRAPHICAL SKETCH

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NAME: **Anthony James Barkovich, MD**

eRA COMMONS USER NAME (credential, e.g., agency login): **BARKOVICH**

POSITION TITLE: **Professor** of Radiology, Pediatrics, Neurology, and Neurological Surgery in Residence

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of CA, Davis	B.S	06/1974	Chemistry
University of CA, Berkeley	M.S.	02/1977	Chemistry
George Wash University, Wash. D.C.	M.D.	05/1980	Medicine
Letterman AMC, San Francisco, CA	Intern	06/1981	Radiology
Letterman AMC, San Francisco, CA	Resident	06/1984	Radiology

A. Personal Statement

As a pediatric neuroradiologist who has specialized in identification, classification and assessment of clinical outcome of patients with developmental disorders and injuries of the developing central nervous system, I feel well qualified to participate in this interesting study. My publications (more than 450 listed in PubMed) on late brain injury resulting from premature birth and injury related to term birth, along with those developmental and acquired disorders of cerebral vasculature and many on genetic disorders (malformative and metabolic) of the cerebrum, midbrain/hindbrain, corpus callosum, and ventral telencephalon, together with my textbook on Pediatric Neuroimaging (6th edition is in press) have resulted in significant advances in the understanding of genetic and environmental effects upon the developing brain. Recent examples include: (1) Pouwels PJ, Vanderver A, Bernard G, Wolf NI, Dreha-Kulaczewski S, Deoni SC, Bertini E, Kolschutter A, Richardson W, Ffrench-Constant C, Kohler W, Rowitch D, **Barkovich AJ**. Hypomyelinating Leukodystrophies: Translational research progress and prospects. Ann Neurol, 2014 Jul;76(1):5-19. doi: 10.1002/ana.24194; (2) Mutch CA, Poduri A, Sahin M, Barry B, Walsh CA, **Barkovich AJ**. Disorders of Microtubule Function in Neurons: Imaging Correlates. AJNR Am J Neuroradiol. 201;37:528-35; (3). Doherty D, Millen KJ, Barkovich AJ. Midbrain and hindbrain malformations: advances in clinical diagnosis, imaging, and genetics. Lancet Neurol 2013;12:381-393 doi: 10.1016/S1474-4422(13)70024-3; and (4) **Barkovich AJ,** Guerrini R, Kuzniecky RI, Jackson G, Dobyns WB. A developmental and embryologic classification for malformations of cortical development. Brain 2012;135:1348-1369. doi: 10.1093/brain/aws019. I have served as a co-investigator for the Vascular effects of Infection in Pediatric Stroke (VIPS) study, providing a developmental lens on the arteriopathies seen in children with stroke. The VIPS renewal aims to determine etiologies of childhood arteriopathies by identifying environmental risk factors (infection) and, potentially, the contribution of the host immune response in order to improve our understanding of the epidemiology and causation of pediatric stroke and, hopefully, help us to reduce its morbidity. *I am a supporter of the T32 program to train residents with an interest in research to learn the proper way to perform thorough and meaningful medical research. I am happy to support the UCSF T32 grant and hope to become an advisor for residents interested in developmental brain disorders.*

B. Positions and Honors

<u>Positions and Employment</u>

1974-1977 UC Berkeley. Electron energy perterbations in strained cyclic hydrocarbons. Prof. P Vollhardt
1976-1989: U.S. Army -- Medical Student, Intern, Radiology Resident, Neuroradiology Fellow, Attending Neuroradiologist. Research on Imaging of anomalous brain development
1986-1989 Neuroradiologist, US Army. Letterman Army Medical Center, San Francisco, CA and Assistant Clinical Professor of Radiology (WOS), University of California, San Francisco
1989-1992: University of California, San Francisco. Associate Professor of Radiology, Pediatrics, Neurology, and Neurological Surgery in Residence
1992-Present: University of California, San Francisco. Professor of Radiology, Pediatrics, Neurology, and Neurological Surgery in Residence

AWARDS:
Goldenson Technology Award, United Cerebral Palsy R&E Foundation, 1998
Peter Emil Becker Award; Outstanding Contributions to Child Neurology/Neuroradiology, German-Austrian-Swiss Society of Child Neurology, 2005
Gold Medalist, American Society of Pediatric Neuroradiology, 2006
Outstanding Lifetime Research Award, American Society of Neuroradiology, 2008
Gold Medal, American Society of Neuroradiology, 2012
Outstanding Achievements in Research Award, Radiological Society of North America, 2012
Distinguished Investigator Award, Academy of Radiology Research, 2013
Faculty Research Lectureship, University of California, San Francisco 2014

C. Contributions to Science

1. Neonatal Brain Injury. A significant amount of pediatric neurological dysfunction can result from premature birth or perinatal brain injury. Although these are common causes of neurological morbidity, the underlying causes have been only poorly worked out. I initially became interested in these disorders because I discovered certain patterns of injury were found on imaging studies (and pathology studies) of encephalopathic term neonates that were related to the type of injury, but then became aware that the patterns were related to many factors: the type of injury; the maturity of the brain; and the timing of the imaging study with respect to the injury (2006). Over the years, we have built a team of researchers at UCSF, composed of neonatologists, child neurologists, neuroradiologists and MR scientists, in order to use imaging as a means of understanding the causes of brain injury and of monitoring the effects of therapies (2011). Our studies of prematurely born children have also yielded important information (2005) and have directly led to changes in the treatment of these babies (2015) and improved outcomes. Currently work in the prematures has shifted to analyses of the cerebellum, which is often affected but the causes and consequences are poorly understood (2011).

a. Kim H, Gano D, Ho ML, Guo XM, Unzueta A, Hess C, Ferriero DM, Xu D, **Barkovich AJ**. Hindbrain regional growth in preterm newborns and its impairment in relation to brain injury. Human Brain Mapping. 2016 Feb;37(2):678-88 PMCID: PMC5094861
b. Cui J, Tymofiyeva O, Desikan R, Flynn T, Kim H, Gano D, Hess CP, Ferriero DM, **Barkovich AJ**, Xu D. Microstructure of the Default Mode Network in Preterm Infants. AJNR Am J Neuroradiol. 2017;38:343-348. Doi:10.3174/ajnr.A4997. PMCID: PMC5309151
c. Gano D, Ho ML, Partridge JC, Glass HC, Xu D, **Barkovich AJ**, Ferriero DM. Antenatal exposure to magnesium sulfate is associated with reduced cerebellar hemorrhage in preterm newborns. J Pediatr 2016;178:68-74. Doi: 10.1016/j.jpeds.2016.06.053. PMCID: PMC5085851
d. Tymofiyeva O, Gano D, Trevino RJ Jr, Glass HC, Flynn T, Lundy SM, McQuillen PS, Ferriero DM, **Barkovich** AJ, Xu D. Aberrant Structural Brain Connectivity in Adolescents with Attentional Problems Who Were Born Prematurely. AJNR Am J Neuroradiol. 2018 Nov;39(11):2140-2147. Doi: 10.3174/ajnr.A5834
e. Guo T, Chau V, Peyvandi S, Latal B, McQuillen PS, Knirsch W, Synnes A, Feldmann M, Naef N, Chakravarty MM, De Petrillo A, Duerden EG, **Barkovich AJ**, Miller SP. White matter injury in term infants with congenital heart disease: Topology & Comparison with preterm infants. Neuroimage. 2019 Jan 15;185:742-749. doi: 10.1016/j.neuroimage.2018.06.004. Epub 2018 Jun 15. PMID: 29890324

2. Malformations of Cortical Development (MCDs). I first became interested in this group of disorders in the 1980s, when their cause and nature was poorly understood. I published the first large series of patients with many MCDs (1987) and then described the clinical and imaging features of many of them including schizencephaly (1988, 1992), band heterotopia (1989, the first description of this entity that was later called "double cortex" by some), hemimegalencephaly (1990), lissencephaly (1991), periventricular nodular heterotopia (1992) and subcortical heterotopia. I was the lead author of the paper that coined the term malformations of cortical development (MCDs) and classified them in 1996 and of the three subsequent updates of the classification that included more and more genetic data (2001, 2006, 2012). In addition, I helped to further understand the mechanistic and genetic abnormalities underlying these malformations, particularly in relation to the processes of proliferation, migration and organization of neurons in the development of the cerebral cortex. These analyses allowed proper classification of "type II lissencephaly" as a cobblestone malformation that is a result of overmigration of neurons through gaps in the pial limiting membrane rather than undermigration of neurons as in lissencephalies due to mutations of genes encoding tubulins or microtubule associated proteins such as LIS1, DCX or NUDL. In addition, we have identified a continuum or malformations associated with mutations of genes encoding proteins active in MTOR, PI3K and AKT pathways.

a. Mutch C, Poduri A, Sahin M, Barry B, Walsh CA, **Barkovich AJ**. Disorders of microtubule functions in neurons: Imaging Correlates. Am J Neuroradiol 2016 Mar;37(3):528-35. doi: 10.3174/ajnr.A4552. PMCID: PMC4792764
b. Desikan R, **Barkovich AJ**. Malformations of Cortical Development. Annals of Neurology 2016 Dec;80(6):797-810. doi:10.1002/ana.24793. PMCID: PMC5177533
c. Tan YL, Kim H, Lee S, Tihan T, Ver Hoef L, Mueller SG, **Barkovich AJ**, Xu D, Knowlton R. Quantitative surface analysis of combined MRI and PET enhances detection of focal cortical dysplasias. Neuroimage 2018;166:10-18. doi: 10.1016/j.neuroimage.2017.10.065. PMCID: PMC5748006 [Available on 2019-02-01]
d. Li Y, Broce IJ, Tan CH, Cuneo D, Hess CP, Dillon WP, Glenn OA, Glastonbury CM, Olney N, Yokoyama JS, Bonham LW, Miller B, Kao A, Andreassen OA, Jernigan T, Dale A, **Barkovich AJ**, Desikan RS, Sugrue LP. Regionally Specific TSC1 and TSC2 gene expression in tuberous sclerosis complex. Scientific Reports 2018 Sep 6;8:13373. doi: 10.1038/s41598-018-31075-4

3. Epilepsy is often associated with/caused by malformations of cortical development, so my interest in MCDs naturally evolved into in interest in epilepsy as I was invited to speak at an increasing number of epilepsy meetings. Some of the work involved building and designing new equipment to help to identify and characterized small lesions that cause medically refractory epilepsy (1997), the most common being focal cortical dysplasias (1997) which has a characteristic MRI appearance that helps its identification and cure (1997). Recent work has shown that many patients with epilepsy have mutations of genes whose protein products are involved in one of the mTOR, PI3K or AKT3 pathways, which are extremely important in growth and development. Many of these lesions can be identified by MR imaging and surgically resected. More important, as these pathways become better understood, the potential exists to intervene within the pathway, downstream from the protein affected by the mutation, thereby treating the symptom without surgical intervention.

a. **Barkovich AJ**, Kuzniecky RI, Bollen AW, Grant PE. Focal transmantle dysplasia: a specific malformation of cortical development. Neurology 1997;49:1148-1152
b. **Barkovich** AJ, Dobyns WB, Guerrini R. Malformations of Cortical Development and Epilepsy. Cold Spring Harb Perspect Med 2015;5:a022392. PMCID: PMC4448581.
c. Nakayama T, Wu J, Galvin-Parton P, Weiss J, Andriola MR, Hill RS, Vaughan D, El-Quessny M, Barry BJ, Partlow JN, Ling J, **Barkovich** AJ, Mochida GH. Deficient activity of alanyl-tRNA synthetase underlies an autosomal recessive syndrome of progressive microcephaly, hypomyelination, and epileptic encephalopathy. Hum Mutat. 2017 May 11. doi: 10.1002/humu.23250. PMCID: PMC5599341 [Available on 2018-10-01]
d. D'Gama AM, Woodworth MB, Hossain A, Bizzotto S, Hatem Yang E, **Barkovich AJ**, Vinters HV, Madsen JR, Mathern GW, Blumcke I, Poduri A, Walsh CW. Somatic Mutations Activating the mTOR

Pathway in Dorsal Telencephalic Progenitors Cause a Continuum of Cortical Dysplasias. Cell Reports 2017, 21, 3754–3766. doi: 10.1016/j.celrep.2017.11.106.PMID:29281825

4. Pediatric Stroke. In our studies of neonatal encephalopathy, we found a subgroup to have focal brain injury from arterial ischemic stroke. This led to my interest in pediatric stroke, and understanding how etiologies, pattern of injury, and outcomes depend on the age of the child at the time of the injury. I have also studied developmental arteriopathies, such as those seen in children with PHACE syndrome. I have participated as a study neuroradiologist in the prospective, international pediatric stroke study, the Vascular effects of Infection in Pediatric Stroke.

a. Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, Ferriero DM, Fullerton HJ, **Barkovich AJ**, Wu YW. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA. 2005 Feb 9;293(6):723-9.
b. Hess CP, Fullerton HJ, Metry DW, Drolet BA, Siegel DH, Auguste KI, Gupta N, Haggstrom AN, Dowd CF, Frieden IJ, **Barkovich AJ**. Cervical and intracranial arterial anomalies in 70 patients with PHACE syndrome. AJNR Am J Neuroradiol. 2010 Nov;31(10):1980-6. doi: 10.3174/ajnr.A2206.
c. Wintermark M, Hills NK, deVeber GA, **Barkovich AJ**, Elkind MS, Sear K, Zhu G, Leiva-Salinas C, Hou Q, Dowling MM, Bernard TJ, Friedman NR, Ichord RN, Fullerton HJ; VIPS Investigators. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the Vascular effects of Infection in Pediatric Stroke Study. Neurology. 2015 Oct 27;85(17):1459-66. doi: 10.1212/WNL.0000000000002065. PMCID: PMC4260818
d. Fullerton HJ, Wintermark M, Hills NK, Dowling MM, Tan M, Rafay MF, Elkind MS, **Barkovich** AJ, deVeber GA; VIPS Investigators. Risk of recurrent arterial ischemic stroke in childhood: A prospective international study. Stroke. 2016 Jan;47(1):53-9. doi: 10.1161/STROKEAHA.115.011173. PMCID: PMC4696877

Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/40855852/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1R21 HD092660 (PI: Li) 07/15/17 - 06/30/19
Simultaneous Multi-slice GABA-edited MRSI in the Developing Brain.
This study will develop methods to localize and quantify GABA in different regions of the developing brain in order to determine the regions in which it is most highly expressed in infants and young children and the effects of abnormal GABA production.
Role: Co-I.

2R01 NS35129 (PI: Walsh) 07/01/14 - 07/31/19
NIH/NINDS 2R01 NS35129
Human Epilepsy Genetics: Neuronal Migration Disorders.
This grant evaluates patients with epilepsy associated with disorders of cerebral cortical development and searches for associated mutations and disorders of molecular pathways
Role: PI of Subcontract to Evaluate Imaging Studies and aid in correlation with genetic mutations found

COMPLETED

P01 NS082330 (PI: McQuillen) 01/01/14 - 12/31/18 see components below
NINDS/ NIH
Repair after Neonatal Brain Injury.
This program uses imaging and clinical parameters to evaluate repair after brain injury in prematures, term-born infants with encephalopathy, and neonates with severe heart defects.
Role: PI of Project 1 (Term infants with encephalopathy).

Project 1 (Barkovich)
Repair after ischemic injury in the term newborn
The broad objectives of this proposal are (1) to use sequential magnetic resonance (MR) studies to segregate different patterns of neonatal brain injury (NBI) that are likely to respond differently to therapeutic hypothermia (TH) and (2) to determine the MR metrics that are most strongly associated with repair after NBI.
Role: PI of Project 1 (Term infants with encephalopathy).

Core B (Xu Project Leader)
Imaging and Neurobehavior
Projects 1-3 of the grant. The overall objective of Service Core B is to ensure accurate and complete imaging for all study subjects across the three projects and to provide a hub for neurobehavioral testing and follow-up coordination.
Role: Co-Investigator

* R01 HD072074 (Xu PI) 12/01/15-11/30/17 0.6 calendar
NIH/NICHHD $ 388,278
Towards Baby Brain Connectome: A study of Newborn Brain Networks
The goal of this Bioengineering Research Grant is to investigate the development of structural and functional connectivity networks in the newborn brain from 26 weeks of gestational age to 1 year of life and correlating with clinical outcome.
Role: Co-Investigator

R01 NS046432 (Barkovich) 9/25/09-8/31/16 (NCE) 4.32 calendar
NIH/NINDS $ 348,372
MRI, MRSI and DTI of Brain Injury in Preterm Neonates
This grant application is focused on evaluating brain injury in premature newborns using 3D MR spectroscopic imaging (MRSI) and diffusion tensor imaging (DTI).
ROLE: PI