Robert Bucelli, MD, PhD

A Novel LPIN1 Mutation Causing Recurrent Rhabdomyolysis in Childhood

Bucelli, Robert C, Connolly, Anne M. Washington University School of Medicine, Department of Neurology.

A three year-old boy was evaluated at our institution for severe recurrent rhabdomyolysis. He was born at term and has normal motor and cognitive development. The first episode of rhabdomyolysis occurred at age sixteen months. He was active at a birthday party and after several hours of play developed an unsteady gait with eventual refusal to walk and tea colored urine. On examination, he was in pain and diffusely weak but with at least antigravity strength in all muscle groups. The general and neurologic examinations were otherwise unremarkable. He has had two recurrences since and has made complete recoveries with supportive care. His neurologic examination and serum CK, remain normal in between episodes.

His laboratory studies included an elevated plasma creatine kinase (CK, peak 498,800 U/L), urine myoglobin (peak 8,277,000 ng/ml), aspartate aminotransferase (peak > 8000 IU/L) and alanine aminotransferase (peak 3,762 IU/L). The remainder of the laboratory studies were normal including cerebrospinal fluid analysis, serum lactate/pyruvate, total and free plasma carnitine, acylcarnitine profile, serum amino acids, leukocytic coenzyme Q10, and peroxisomal profile. Cardiac and abdominal ultrasounds were normal. Brain MRI with spectroscopy was normal. Pathogenic mutations were not present in RYR1 or PYGM. A muscle biopsy was obtained 6 weeks after the second episode and revealed changes consistent with recent rhabdomyolysis and moderately increased lipid content but with normal mitochondrial stains and enzymatic activities.

Mutations in LPIN1 have recently been identified as a relatively common cause of recurrent acute myoglobinuria of childhood (Zeharia et al., 2008). LPIN1 sequencing in our patient demonstrated compound heterozygosity for a novel c.1904 T>C (p.Leu635Pro, likely pathogenic) variant and a previously reported genomic deletion of exons 18-19. Subsequent studies have suggested that LPIN1 mutations ought to be regarded as a major cause of severe myoglobinuria of childhood (Michot et al., 2010). The associations between lipin-1 deficiency and recurrent myoglobinuria of childhood are the subject of ongoing investigations and have implications for other myopathies, including statin-associated myopathy. Our experience would support recent proposals advocating screening for LPIN1 mutations in the early stages of the metabolic workup of patients with recurrent myoglobinurias.

B. Keith Day, MD, PhD

Investigations of Cytoskeletal Changes in the Hippocampus and Cortex Following Kainate-Induced Seizures

Kainate (KA)-induced seizures in mice cause morphological changes in dendritic spines seen by 2-photon microscopy as well as changes in actin depolymerization. Dendritic spine stabilization has been proposed as a novel therapeutic target for preventing epileptogenesis or epilepsy-associated disability. This work tested the hypothesis that dendritic spine loss and beading seen following severe KA-induced seizures are associated with specific cytoskeletal protein changes in a time-dependent fashion that can be detected using total protein levels measured by Western blotting. C57Bl6 mice were injected with either KA or saline and sacrificed at 0, 1, 4, and 24 hours. Bilateral hippocampi and neocortices were prepared and Western blots performed to identify total protein changes for cytoskeletal proteins tubulin, MAP2, and EB3. Total actin levels were also evaluated to confirm equivalent protein loading. Using Western blotting, there were no apparent changes in total protein in hippocampus or cortex in tubulin, MAP2, or EB3 following KA-induced severe seizures in this model at the investigated time points.
Gabriela deBruin, MD

Kikuchi-Fujimoto disease presenting with aseptic meningitis

de Bruin, Gabriela
Washington University School of Medicine, Department of Neurology.

Introduction: Kikuchi-Fujimoto disease (KFD) is a self-limited condition of unknown etiology characterized by cervical lymphadenopathy and fever that typically affects young women. CNS involvement is uncommon in KFD. Diagnosis requires pathology showing histiocytic necrotizing lymphadenitis and an appropriate clinical presentation.

Case Report: A 54-year-old African-American male presented with 3 months of fevers, night sweats, weight loss, headaches and altered mental status. General exam was notable for cervical lymphadenopathy and a maculopapular rash involving his trunk and upper extremities. Neurologic exam revealed a somnolent man, disoriented to the date, with decreased attention and concentration but no focal neurological deficits. His mental status fluctuated and seemed to be worse with high fevers. CSF was consistent with an aseptic meningitis. Imaging of the chest, abdomen and pelvis showed diffuse lymphadenopathy in the neck, mediastinal and gastrohepatic regions. A lymph node biopsy revealed findings consistent with KFD. The patient’s symptoms completely resolved over 3 months.

Discussion: KFD is a rare disease that may initially be mistaken for various benign and malignant diseases such as SLE, tuberculosis or lymphoma. As exemplified by this case, it is not limited to the young Asian female demographic in which it was originally described. CNS involvement occurs in less than 10% of cases of KFD with aseptic meningitis being the most common CNS manifestation. Absence of meningeal signs is a frequent negative finding (45%) in KFD-associated meningitis. Meningitis has been reported to be more common in male patients with KD such as in this case. Like other symptoms in KFD, meningitis is self-limited and no sequelae have been reported in the literature.

Conclusions: KFD should be considered in the differential diagnosis of aseptic meningitis in young patients with diffuse lymphadenopathy when evaluations for infection and malignancy have been negative.

Kristin Guilliams, MD

Cessation of Refractory Status Epilepticus with Mild Hypothermia

Kristin Guilliams (Kelvin Yamada, Jose Pineda)

A 10 year old girl was transferred to St. Louis Children’s Hospital from a referring hospital with a three week history of refractory status epilepticus. She had been managed with multiple anti-epileptic medications, including 2 periods of pentobarbital burst suppression coma. Her seizures proved refractory to all interventions. She continued to have focal seizure activity upon admission. This is documented on EEG, and ceased approximately seventy-five minutes after reaching goal bladder temperature of 34 degrees Celsius. Seizures did not recur after rewarming or during the remainder of her two month hospitalization. She was cooled with an external cooling device and no adverse events of hypothermia were observed. While this institution has previously published cases of treating refractory status epilepticus with hypothermia in adults, hypothermia has not yet been reported as a treatment used for refractory status epilepticus in children.
Karan Johar, MD

"Generalized pruritus after recovery from traumatic brain injury successfully treated with neuropathic pain agents."

David Brody, MD/PhD and Karan Johar, MD

Generalized pruritus after exogenous causes such as central nervous system insult could, in theory, result from brain structural changes, causing misperception of normal stimuli. This phenomenon has been documented in brain tumor and stroke patients. However, it has not, to our knowledge, been documented after traumatic brain injury. Here, we present the first reported case of traumatic brain injury that resulted in generalized pruritus and its successful management using an anti-epileptic (pregabalin) and serotonin-norepinephrine reuptake inhibitor (duloxetine).

Naim Khoury, MD

Clinical and MRI Characteristics of Ischemic Stroke Patients with NIHSS of 0

Naim Khoury, Peter Panagos, David K. Tan, Jennifer A. Williams, Jin-Moo Lee and Andria L. Ford.

Presented at an oral platform at the International Stroke Conference 2011, Los Angeles, CA.

Background: The NIHSS is widely used for acute stroke treatment evaluation. Patients with low NIHSS score are often excluded from treatment and recent reports suggest that they may have significant disability. We examined a cohort of MRI-confirmed ischemic stroke patients with NIHSS score of 0 at presentation to characterize clinical and MRI findings.

Methods: Data on all stroke patients admitted to a large academic medical center was collected starting in 2003 as part of a prospective database. Ischemic stroke patients with NIHSS = 0, presenting within 24 hrs of symptom onset with MRI-confirmed strokes were retrospectively reviewed (NIHSS0). Patients with resolving deficits or late presentation were excluded. A matching set of patients with NIHSS = 1-3 were randomly selected for comparison (NIHSS1-3). Clinical and MR characteristics were evaluated and compared between the two groups using Fisher’s Exact test, p<0.05 required for significance.

Results: Of 959 ischemic stroke patients with DWI lesions (DWI+), 96 had NIHSS=0; 24 had fixed stable deficits at presentation; a comparison group of 25 patients was randomly selected from the DWI+ patients with NIHSS = 1-3 using the same exclusion criteria. Chief complaints (CC) were different in the two groups. The most common CC for NIHSS0 patients was “dizziness” (37.5% vs 12.0%, p=0.05), while CC of “speech difficulty” (36.0% vs 12.5%, p=0.02) or “blurred vision” (24.0% vs 0.0%, p=0.02) was most common for NIHSS1-3 patients. There was no difference between groups with regard to laterality (left vs right) or anterior vs posterior circulation. There was a trend for the patient with NIHSS=0 to have cerebellar strokes. There was no statistically significant difference in the total volume of infarct of the two groups (8.2 cc vs 6.9 cc) and the proportion of patients discharged to acute rehabilitation was not statistically different either (21.6% vs 16.7%).

Conclusions: Ischemic stroke patients with NIHSS of 0 have different clinical and imaging characteristics compared to patients that score on the scale. CC of “dizziness” is more common; the patients in the two groups had equal volume of infarcted tissue and the same probability of being discharged to acute rehabilitation. These results underscore limitations of the NIHSS for assessing acute neurological deficits, and should be taken into consideration when making acute treatment decisions.
Andrew Lin, MD

Does Medical Student Neurology Knowledge Correlate with Performance on the Neurological Examination?

OBJECTIVE: The objective of this study is to determine the correlation between medical student knowledge of neurology, as measured by performance on the NBME Clinical Neurology Subject Examination, and performance on the neurological examination.

BACKGROUND: The Clinical Neurology Subject Examination (shelf exam) is a standardized multiple-choice exam that is written and distributed by the National Board of Medical Examiners (NBME). The shelf exam is specifically designed to assess knowledge, and Clerkship directors use the Shelf to broadly evaluate student performance on the neurology clerkship.

DESIGN/METHODS: The subjects in this retrospective analysis are students from the class of 2008, 2009, and 2010 at Weill Cornell Medical College who followed a four-year schedule from matriculation to graduation. During their third or fourth year of medical school, these students were required to participate in the neurology clerkship and take the neurology shelf exam. In this study, the performance of these students on the neurology shelf is correlated with their ability to perform a neurologic examination as assessed by an objective structured clinical exercise (OSCE) using standardized patients (SPs) administered during fourth year. Performance on the neurologic examination was scored on a scale of 0.0 to 6.0 by the SPs conducting the OSCE according to a checklist of 20 items that carry equal weight.

RESULTS: No correlation was found between shelf and neurology physical examination (NPE) scores (r = 0.10). On subgroup analysis, there was no correlation between shelf and NPE scores among the students who had started or completed the neurology clerkship prior to OSCE administration (r = -0.032).

CONCLUSIONS: Student performance on an assessment of the neurologic examination is independent of student performance on the neurology shelf exam. Clerkship evaluation should incorporate additional tools, such as simulated patient exercises, specifically for assessing student clinical skills.

Mahesh Mohan, MD


Mahesh Mohan, MD, Sindhu Jacob, MD, FAAPMR, Rob Fucetola, PhD, ABPP.

Division of Stroke and Brain Injury Rehabilitation, Washington University in St. Louis.

Abstract:

Introduction: Anorexia and refusal to feed can be a management problem in a Traumatic Brain Injury (TBI) patient. Management issues gets complicated because of ethical dilemma of respecting patient autonomy versus difficulty in determining decision making capacity of brain injured patient. Can these symptoms be considered as forerunners of impending psychotic behavior is worth exploring.

Case Description:

34 y/o Male, with no pre-injury personality disorder, suffered a bi-frontal moderate TBI. He showed significant refusal to eat leading to 80 lbs. weight loss in a month. This was followed by significant psychotic behavior and hostility leading to involuntary admission to an Inpatient Psychiatric Unit. Combination of cognitive behavioral interventions and pharmacological measures helped resolve the situation.

Discussion:

Management of a TBI patient in the rehabilitative phase can often be complicated by behavioral problems. Management decisions can get delayed because of difficulty determining the competency of the brain injured patient. Timely identification of issues and interventions both cognitive as well as pharmacological, are crucial for patient and caregiver wellbeing and safety. This case report is an effort to increase the awareness of difficult management issues in TBI population.
Clinical and Diagnostic Markers of Sporadic Creutzfeldt-Jakob Disease (sCJD) at Barnes-Jewish Hospital from 2005-2010

Patrick, Erica1†, Bucelli, Robert C1†, Wang, Leo H.1†, Alvarez III, Enrique A.1, Lim, Miranda1,3, DeBruin, Gabriela1, Sharma, Victoria1, Dahiya, Sonika1, Benzinger, Tammy2, Ward, Beth A.1, Ances Beau M1 for the Washington University School of Medicine Rapidly Progressive Dementia Resident Research Consortium.

1Washington University School of Medicine, Department of Neurology.
2Washington University School of Medicine, Department of Radiology.
3University of Pennsylvania, Department of Medicine
4Washington University School of Medicine, Department of Pathology

† = These authors contributed equally to the work.

Objectives: Sporadic Creutzfeldt-Jakob Disease (sCJD) is a rapidly progressive dementia (RPD) that is difficult to diagnose. Definitive diagnosis requires tissue confirmation via biopsy or autopsy. The recent additions of magnetic resonance diffusion-weighted imaging (MRI-DWI) and cerebrospinal fluid (CSF) biomarkers to the diagnostic evaluation of patients suffering from sCJD have helped to improve its pre-mortem diagnosis. In this study we set out to assess whether diffusion-tensor imaging (DTI) and/or polysomnography (PSG) are of any utility in further distinguishing sCJD from other RPDs.

Methods: A resident-based research consortium conducted an evaluation of all patients presenting to our institution for evaluation of a RPD between 2005 and 2010. In total we characterized the clinical and diagnostic markers (including MRI, CSF and EEG) of 30 patients, 17 sCJD patients (15 confirmed, 2 probable) and 13 patients suffering from a RPD of alternate etiology. When possible, all patients also underwent DTI imaging. DTI images from 18 non-demented control patients were analyzed for comparison purposes. Patients in both groups were also screened for sleep-related complaints and polysomnograms were obtained, when clinically indicated, to characterize any sleep-related pathology.

Results: Elevated levels of tau and 14-3-3 in CSF and typical DWI changes on MRI were significantly more common in the sCJD group. No differences were observed between groups with respect to demographics or EEG findings. DTI analysis revealed significant decreases in mean diffusivity (MD) in the caudate and pulvinar in sCJD patients compared to RPD patients and controls. Sleep symptoms were more prevalent in the sCJD group but most patients with rapidly progressive dementia (both sCJD and RPD groups) had disorganized sleep on PSG.

Conclusions: Our results suggest that DTI-MRI and a multimodal evaluation for sleep-related pathology may serve as additional non-invasive diagnostic tools in distinguishing sCJD from other RPDs.
**Seth Perlman, MD**

**Chromosome 16p11.2 deletion syndrome associated with neuroblastoma related opsoclonus-myoclonus-ataxia syndrome**

Seth Perlman, MD (Michael Noetzel, MD)

A 23-month-old girl presented with a one-week history of progressive eye twitching, head shaking, clumsy limb movements, and gait unsteadiness. Her general physical exam revealed only subtle facial dysmorphic features. Her neurological examination was notable for irritability, lack of speech or ability to follow commands, bilateral horizontal nystagmus, marked head titubation, ataxia and dysmetria affecting her bilateral upper extremities, and gait ataxia. Extensive laboratory evaluations were unrevealing. Brain magnetic resonance imaging (MRI) was normal. Abdominal computerized tomography revealed a left extra-adrenal para-aortic mass that was subsequently resected. Pathologic examination revealed nodular ganglioneuroblastoma (INSS stage 2B) with polysomy 2 in one tissue subset and no evidence of N-myc gene amplification. Serum paraneoplastic antibody panel was normal. She was diagnosed with neuroblastoma related opsoclonus-myoclonus-ataxia syndrome and treated with prednisolone, intravenous gammaglobulin (IVIG), and cyclophosphamide. Subsequent to this diagnosis further concerns were raised regarding premorbid developmental delay and symptoms concerning for an autistic spectrum disorder. Chromosomal microarray was sent and revealed a 672Kb deletion at chromosome 16p11.2, which has been reported in individuals with autism, aortic valve disease, seizures and mild mental retardation. To date, no other patients have been reported with this deletion syndrome and cancer.

**Peiqing Qian, MD**

**Multiple Sclerosis T2 Lesions Which Disappear May Still Have Persistent Tissue Injury**

Peiqing Qian, Samantha Lancia, Junqian Xu, Jeffrey H. Huang, Anne H. Cross, Leo J. Wolansky, Stuart Cook, Diego Cadavid, Robert T. Naismith

**OBJECTIVE:** Determine whether new T2 lesions which revert to “normal-appearing white matter”, recover to their pre-lesion baseline levels by diffusion tensor imaging, a surrogate of tissue integrity.

**BACKGROUND:** MRI has high sensitivity to detect MS plaques by T2-weighted sequences. Some T2 lesions have been noted to disappear over time, but the frequency and clinical significance of lesion recovery to T2 isointensity has not been established.

**DESIGN/METHODS:** 75 subjects with treated relapsing MS were followed for over 2 years. MRIs were obtained monthly, with 1236 total scans, and a median 14 scans per subject. The MRI was optimized to detect inflammatory lesions by triple-dose/delayed gadolinium at 3 Tesla. New T2 hyperintensities (T2Hs) were tracked and categorized as to whether they persisted for at least 12 months, or recovered to isointensity on the FLAIR, PDW and T2W images. Radial diffusivity at baseline, lesion onset and monthly follow up were analyzed.

**RESULTS:** 824 new T2Hs have been analyzed. Of newly formed T2 lesions, 50.1% disappeared on FLAIR images with subsequent follow-up (transient T2Hs), 27.5% persisted for at least 12 months (chronic T2Hs), and 22.4% had insufficient follow-up for classification. Of the transient T2H lesions, 77.2% reverted to isointense within 3 months of onset. Persistent FLAIR were more likely to enhance for >1 month compared to transient FLAIR (p<0.001). At lesion onset, RD ratio for both transient and persistent FLAIR lesions became elevated above baseline. Transient FLAIR had a sustained lower RD ratio than persistent FLAIR. At 12 months, RD ratio for both transient and persistent FLAIR lesions remained elevated compared to baseline.

**CONCLUSIONS:** Transient T2H are not uncommon when observing monthly MRI scans. FLAIR sequences may underestimate the T2H persistence. Complementary information can be provided by including PDW and T2 sequences. Lower RD ratio distinguishes transient from chronic T2H lesions at lesion onset. Radial diffusivity ratio may not return to baseline in transient T2Hs, suggesting persistent injury despite FLAIR recovery into ‘normal-appearing white matter’.
Lupus cerebritis presenting as other neurodegenerative diseases. Two cases from the neurology inpatient service.

TR Sampson, RK Joshi, R Brasington

Polymerase Gamma Disease Associated with Severe Headache, Stroke-like Episode, Intractable Epilepsy with Later-Onset Progressive External Ophthalmoplegia.

Mutations in the mitochondrial DNA polymerase, polymerase gamma 1 (POLG1) are the most common group of mitochondrial diseases and have a wide phenotypic presentation. These can vary from progressive external ophthalmoplegia with relatively slow progression of other deficits to the much more severe childhood-onset progressive encephalopathy with intractable epilepsy and hepatic failure, Alpers-Huttenlocher syndrome. Here we describe a patient with homozygous POLG1 mutation with a severe phenotype disease presentation in adulthood. This presentation emphasizes the importance of a high index of suspicion for this heterogeneous group of disorders.
Amy Viehoever, MD

CNS disease in CMT-X: a case presentation and ongoing study of MRI imaging in a large family with CMT-X

X-linked Charcot-Marie-Tooth (CMT-X) is an X-linked dominant hereditary peripheral neuropathy caused by mutation in the GJB1 gene that codes for the connexin 32 protein which is highly expressed in Schwann cells as well as oligodendrocytes. Central nervous system involvement with white matter changes on magnetic resonance imaging (MRI) has been reported in this condition. We report the case of a 12-year-old, previously well boy with a stuttering presentation of left hemiparesis and dysphasia over a 3 day period. A brain MRI found white matter signal changes affecting the corpus callosum and periventricular areas with a posterior predominance similar to previous reported cases. The majority of his clinical symptoms resolved prior to discharge. Family history revealed an extensive family history of CMT with at least 13 members affected. Electrophysiological and genetic studies confirmed the diagnosis of CMT-X with a arginine to tryptophan substitution at codon 142 in the GJB1 gene, a known disease causing mutation, but one which has not yet been reported to be associated with CNS involvement. A repeat brain MRI one year later showed faint residual white matter changes. We have initiated a study of CNS involvement in this large family with CMT-X to understand the relationship between genotype and phenotype of CNS white matter involvement.

Tuhin Virmani, MD, PhD

Clinical Reasoning: A young adult presents with focal weakness and hemorrhagic brain lesions

Tuhin Virmani MD, PhD 1; Ashima Agarwal MD 2; Eric C Klawiter MD 1

1 Department of Neurology and 2 Department of Pathology, Washington University, Saint Louis, MO
Lirong Zhu, MD, PhD

Marchiafava-Bignami Disease in a Non-alcoholic Female Receiving Cisplatin

Lirong Zhu, MD, PhD1, Joshua Shimony, MD2, James E. Galvin, MD, MPH1

1Department of Neurology, 2Malinckrodt Institute of Radiology, Neuroradiology Section, Washington University School of Medicine, St. Louis, MO, United States, 3Center of Excellence on Brain Aging, New York University Langone Medical Center, New York, NY, United States.

OBJECTIVE: To describe the first report of Marchiafava-Bignami disease (MBD) triggered by Cisplatin in a non-alcoholic female.

BACKGROUND: MBD is a rare neurological disorder traditionally seen in chronic alcoholics with psychiatric disturbances, interhemispheric disconnection symptoms, impaired consciousness and lesions of corpus callosum on brain magnetic resonance imaging (MRI).

DESIGN/METHODS: Case report.

RESULTS: A 51-year-old woman with stage IV basoloid carcinoma of the anus without brain metastasis presented with agitation, visual hallucinations, confusion, aphasia and apraxia after receiving Cisplatin and 5-fluorouracil (5-FU). Brain MRI revealed a new hyperintense signal in the splenium of the corpus callosum on T2 and diffusion-weighted image with corresponding hypointense signal on the apparent diffusion coefficient map, consistent with MBD. She returned to baseline in a few weeks after vitamin supplementation and discontinuation of Cisplatin and 5-FU. Follow-up brain MRI in 9 weeks showed complete resolution of the signal abnormality in the corpus callosum. 5-FU has been reported to cause encephalopathy with similar reversible MRI findings. However, she previously received 5-FU twice and brain MRI was normal after each 5-FU Infusion. Other etiologies causing similar brain MRI findings were excluded, including ischemia, encephalitis, epilepsy receiving antiepileptic drugs, human immunodeficiency virus infection, lymphoma, multiple sclerosis and severe malnutrition. She previously had never received Cisplatin, which is well known to cause reversible demyelinating peripheral neuropathy. Cerebral cortex and subcortical white matter lesion have been reported to be associated with Cisplatin, but not the deep cerebral white matter. It is likely that Cisplatin or a combination of Cisplatin and 5-FU can also induce demyelination in the white matter of corpus callosum.

CONCLUSIONS: We report the first case to develop reversible lesion in the splenium of the corpus callosum suspected to be triggered by Cisplatin. We believe it is important to consider and treat MBD in patients developing encephalopathy after chemotherapy, since it is potential reversible.

Lirong Zhu, MD, PhD

Investigation of the Influence of Age, Family History of Alzheimer’s Disease, and APOE4 Allele on Various Cerebrospinal Fluid Biomarkers in the Adult Children Study

Lirong Zhu, MD, PhD1, David M. Holtzman, MD, PhD2,3, John C. Morris, MD1,2, Anne M. Fagan, PhD1,2,3

1Department of Neurology, 2Charles F. and Joanne Knight Alzheimer’s Disease Research Center, 3Hope Center for Neurological Disorders, Washington University School of Medicine, St. Louis, MO, United States

Background: Alzheimer’s disease (AD) pathology is estimated to begin ~10-20 years prior to cognitive symptoms; thus, it is imperative to identify biomarkers that will distinguish individuals early in the disease process, so emerging therapies have the best chance to preserve normal brain function. Cerebrospinal fluid (CSF) proteins known to be related to the AD pathologic hallmarks of amyloid plaques and neurofibrillary tangles, Aβ42 and tau, respectively, have shown promise as diagnostic and prognostic AD biomarkers; CSF Aβ42 decreases in individuals with amyloid plaques in the brain, likely due to its sequestration in plaques, whereas CSF tau increases in AD presumably reflecting the presence of tangles and/or neurodegeneration. CSF tau/Aβ42 ratio has been established as a best-performing biomarker to discriminate individuals with AD dementia (Clinical Dementia Rating, CDR, >0) from those who are cognitively normal (CDR 0). However, how early in the disease process such CSF changes are detectable and the effects of AD risk factors on these CSF changes are unclear.

Objective: To investigate the influence of strong AD risk factors: age, family history (FH) of AD and APOE4 allele, on CSF Aβ42, tau and the tau/Aβ42 ratio by cross-sectional comparison between middle-aged individuals.

Methods: 243 cognitively normal (CDR 0) 43- to 76-year old individuals with known AD risk profiles, i.e., having a positive or negative FH of AD (FH+ vs FH−), as well as APOE genotype (the strongest genetic risk factor for AD) (E4+ vs E4−), were recruited into the Adult Children Study (ACS) at the Knight Alzheimer’s Disease Research Center at Washington University. The CSF samples were analyzed for Aβ42 and tau by commercial enzyme-linked immunosorbent assay (ELISA). The Pearson’s Correlation was used to study the correlation of CSF Aβ42, tau, and tau/Aβ42 with age.

Results: CSF Aβ42 decreased significantly with age in FH+ (r=0.269, p=0.002) but not FH− (r=0.082, p=0.384) individuals, as well as in both E4+ (r=0.225, p=0.027) and E4− (r=0.205, p=0.013) individuals. In both E4+ and E4− individuals who were FH+, the level of CSF Aβ42 still decreased significantly with age (r=0.333, p=0.006 and r=0.322, p=0.011, respectively), whereas such a decrease was not observed in FH− individuals (r=0.105, p=0.573 and r=0.065, p=0.552, respectively), indicating other non-APOE genetic factors may play a role in the age-related decreases in CSF Aβ42. The levels of CSF tau and tau/Aβ42 significantly increased with
age in both FH+ and FH- groups (p<0.01). However, CSF tau and tau/Aβ42 increased significantly by age in the FH+ E4+ group (r=0.329, p=0.007, and r=0.477, p=5.2E-5, respectively), but not in the FH+ E4- group (r=0.116, p=0.372, and r=0.360, p=0.10, respectively), indicating that APOE genotype influences the age-related increases of CSF tau, especially that of CSF tau/Aβ42, in individuals with a positive family history of AD.

**Conclusion:** The present data, albeit cross-sectional, suggest that the development of AD pathology in the preclinical period is influenced by both FH and APOE genotype. A positive FH for AD is associated with age-related increases in CSF tau and tau/Aβ42 and decreases in CSF Aβ42. Presence of the APOE4 allele does not influence the age-related decrease in CSF Aβ42, but does influence the increase in CSF tau with an even stronger influence on the increase of CSF tau/Aβ42 suggesting that middle-aged individuals who possess both risk factors (positive for FH and APOE4) may already be on the path towards developing AD. Analysis of longitudinal changes in biomarker levels and cognition within individuals over time will be necessary to evaluate the utility of such preclinical changes in predicting future cognitive decline.