**Investigating the Biological Context of Metabolomic Changes in Alzheimer’s Pathology Using Predictive Pathway Enrichment**

**K Dewan1**, **K Dewan**1, S Sinha2, B Willard2, J Pillai3, J Leverenz3, L Bekris4, T Dey5, **SW Pimplikar**1

1Dept. of Neurosciences, Lerner Research Institute, 2Metabolomics Core, Dept. of Cell Molecular Medicine, Lerner Research Institute, 3Lou Ruvo Center for Brain Health, Neurological Institute, 4Department of Genomic Medicine, Lerner Research Institute, 5Division of Quantitative Health Sciences

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder with multifactorial etiology and is the fifth leading cause of death in US for those above 65. There has been renewed interest in proactive diagnosis of amnestic mild cognitive impairment (aMCI), the earliest clinical presentation of AD. Though patients with aMCI are at higher risk for developing AD, the progression from aMCI to AD is not always inevitable, and the mechanism for conversion has not been clearly elucidated. Therefore it is of interest to explore biomarkers specifically characteristic of AD in aMCI patients. While B-amyloid and tau proteins have been well established as AD biomarkers, recent advances in metabolomics provides the opportunity to explore more accessible biomarkers predictive of AD. We previously characterized distinct metabolic profiles of AD and age-matched controls through OPLS-DA analysis. The objective of this investigation was to further investigate the biological context of these significantly different metabolites by data mining and pathway enrichment tools. Metabolite data was collected from plasma and CSF samples from 6 AD patients and 6 age-matched controls by LC-MS. The top 50 LC-MS features by significance and fold chance were putatively identified using Metlin, Kegg, PubChem, and Human Metabolome Databases, and were subjected to metabolomic and canonical pathway analyses using Ingenuity Pathway Analysis (Ingenuity Systems, Redwood City, CA). Our data found significant differences in total of 249 blood plasma and 28 CSF metabolites. IPA canonical analysis of putatively identified metabolites indicated a dysregulation of key amino acid and phospholipid pathways in CSF and plasma. The data most notably suggested a role for sphingolipid metabolism/ceramide signaling in AD-related apoptosis. These preliminary results provide the basis for investigating sphingosine among other possible biomarkers in aMCI patients in order to predict further progression.

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Primary Author Contacts:

Krish Dewan  
M.D. Candidate, 2020  
College of Medicine  
Northeast Ohio Medical University   
[kdewan@neomed.edu](mailto:kdewan@neomed.edu)

Karan S. Dewan  
M.D. Candidate, 2020  
College of Medicine  
Northeast Ohio Medical University   
[kdewan1@neomed.edu](mailto:kdewan1@neomed.edu)

Sanjay Pimplikar, Ph.D.  
Associate Staff  
Dept of Neurosciences, Lerner Research Institute, Cleveland Clinic  
[pimplis@ccf.org](mailto:pimplis@ccf.org)