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Featured Article

Metabolic network failures in Alzheimer's disease—A biochemical road map

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Abstract

Introduction: The Alzheimer's Disease Research Summits of 2012 and 2015 incorporated experts from academia, industry, and nonprofit organizations to develop new research directions to transform our understanding of Alzheimer's disease (AD) and propel the development of critically needed therapies. In response to their recommendations, big data at multiple levels are being generated and integrated to study network failures in disease. We used metabolomics as a global biochemical approach to identify peripheral metabolic changes in AD patients and correlate them to cerebrospinal fluid pathology markers, imaging features, and cognitive performance.

Methods: Fasting serum samples from the Alzheimer's Disease Neuroimaging Initiative (199 control, 356 mild cognitive impairment, and 175 AD participants) were analyzed using the AbsoluteIDQ-p180 kit. Performance was validated in blinded replicates, and values were medication adjusted.

Results: Multivariable-adjusted analyses showed that sphingomyelins and ether-containing phosphatidylcholines were altered in preclinical biomarker-defined AD stages, whereas acylcarnitines and several amines, including the branched-chain amino acid valine and α-aminoadipic acid, changed in symptomatic stages. Several of the analytes showed consistent associations in the Rotterdam, Erasmus Rucphen Family, and Indiana Memory and Aging Studies. Partial correlation networks constructed for $A\beta_{1-42}$, tau, imaging, and cognitive changes provided initial biochemical insights for disease-related processes. Coexpression networks interconnected key metabolic effectors of disease.

Discussion: Metabolomics identified key disease-related metabolic changes and disease-progression-related changes. Defining metabolic changes during AD disease trajectory and its relationship to clinical phenotypes provides a powerful roadmap for drug and biomarker discovery.

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1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia. An anticipated 136 million people will be affected by dementia by 2050, presenting major global health and economic challenges. There are currently no treatments that modify AD; hence, AD remains the largest unmet medical need within neurological disorders [1,2].

Many biochemical processes are affected in AD, including amyloid precursor protein metabolism, phosphorylation of tau protein, oxidative stress, impaired energetics, mitochondrial dysfunction, inflammation, membrane lipid dysregulation, and neurotransmitter pathway disruption [3,4]. Impaired cerebral glucose uptake occurs decades before the onset of cognitive dysfunction in AD [5], and neurotoxicity associated with Aβ is thought to participate in impaired neuronal energetics including mitochondrial dysfunction and release of reactive oxygen species. Growing evidence supports the concept that insulin resistance can contribute to AD pathogenesis, and therefore, AD could be regarded as a metabolic disease mediated in part by brain insulin and insulin-like growth factor resistance [3]. Mapping the trajectory of biochemical changes in AD is therefore becoming a priority as filling knowledge gaps about disease mechanisms and their link to metabolic processes can lead to developing much-needed biomarkers and therapies [3]. How does peripheral metabolism, diet, gut microbiome, and exposome impact the metabolic heath of the brain, and thus cognitive function? Which pathways are affected by genes that have been implicated in AD, such as presenilin 1 (*PSEN1*) and *PS2* or apolipoprotein E (*APOE*) genes? Biochemical information elucidating these questions is critical for developing drugs that target enzymes and transporters which regulate metabolism.

Metabolomics provides powerful tools for mapping global biochemical changes in disease and treatment [6–10]. In contrast to classical biochemical approaches that focus on single metabolites or reactions, metabolomics and lipidomics approaches simultaneously identify and quantify hundreds to thousands of metabolites [11–19]. Measurement of large numbers of metabolites enables network analysis approaches and provides means to identify critical metabolic drivers in disease pathophysiology [20]. Initial small-scale metabolomics studies in AD have highlighted metabolic alterations including ceramide–sphingomyelin pathways [10], glycerophosphatidylcholines (*aa* = diacyl, *ae* = acyl–alkyl) [PC] [15,21], PE plasmalogens [22,23], amines [24], and mitochondrial defects [25] among others [13,14]. Metabolic networks have linked central perturbations in norepinephrine and purines with elevated cerebrospinal fluid (CSF) tau, and changes in tryptophan and methionine to decreased Aβ levels [18]. More recently, the ARIC Neurocognitive Study identified PC aa C36:1 as being linked to lower risk of dementia; however, no metabolite from the panel measured added significantly to prediction of dementia beyond routine clinical variables [26]. A recent plasma–pathology correlative study found that plasma ceramides C16:0, C18:1, C20:0, and C24:1 and monohexosylceramides C18:1 and C24:1 were

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