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Abstract Title: Identifying Metabolic Markers Implicated in Multiple Sclerosis Clinical Onset and Severity

Abstract Category: 2. PATHOLOGY & PATHOGENESIS OF MS - 2.1 Pathology

Preferred Presentation Type: Poster presentation only

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Background

Multiple sclerosis (MS) is a complex disease in which genetic susceptibility interacts with environmental factors to shape disease risk and drive long-term progression. Circulating metabolites (including lipids) are small molecules that can reflect these dynamic interactions. While essential for elucidating MS pathogenesis, the systematic characterization of metabolic signatures from clinical onset through long-term progression remains under-explored.

Objectives/Aims

To identify circulating metabolites associated with MS onset and severity, and to contextualize these findings within MS-related, multi-layered biological pathways.

Methods

In a large MS case-control study longitudinally followed up to 15 years (*n*=263 at baseline; 230 at 5 years; 226 at 10 years; 189 at 15 years) and 506 matched controls at baseline, we conducted untargeted serum metabolomic and lipidomic profiling using liquid chromatography-mass spectrometry (LC-MS/MS). Various statistical analyses were undertaken including variance components analysis, metabolome/lipidome-wide association studies for MS onset and severity (age-adjusted MS severity score), enrichment and network analyses.

Results

A substantial proportion of variance in MS onset was captured by the metabolome (22%, $N_{metabolite}$=735, P=7.4x10^{-6}) and lipidome (16%, N_{lipid}=539, P=1.6x10^{-6}) after adjusting for experimental and demographic covariates. We identified 57 metabolites and 81 lipids significantly associated with MS clinical onset and 4 metabolites and 1 lipid significantly associated with disability severity (P_{FDR}<0.05) after adjusting for covariates. Enrichment analysis implicated lipid mediated signalling and membrane phospholipid remodelling as the prominent processes associated with MS clinical onset. Using the MS-relevant metabolites, we constructed a gene-metabolite network comprising 201 genes that interact with multiple significant metabolites. Functional pathway analysis of these genes revealed significant enrichment in neuroinflammation and glutamatergic signalling pathways.

Conclusion

This work identified an interconnected network of circulating metabolic signatures associated with MS clinical onset and disability severity. The set of identified signatures converge onto known bioactive lipid pathways, providing biological insights into MS pathophysiology and supporting further mechanistic study of these candidate targets to accelerate biomarker development and therapeutic targeting.

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