Bile Acid Metabolism is Altered in Multiple Sclerosis and Supplementation Leads to Amelioration of Neuroinflammation

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Objective:
To determine alterations in circulating bile acid (BA) metabolites in multiple sclerosis (MS) and determine the effects of a BA – tauroursodeoxycholic acid (TUDCA) on neuroinflammation.
Background:
BA are cholesterol metabolites that have several functions, including direct effects on immune and glial cells. Whether BA metabolism is affected in MS is not known.
Design/Methods:
We enrolled discovery (50 healthy control [HC]/50 RRMS/50 PMS), validation (75 HC/50 RRMS/125 PMS) and pediatric (31 HC/31 MS) cohorts. We utilized global (discovery and pediatric) or targeted (validation) metabolomics analyses to measure BA metabolites. We calculated pathway deregulation scores (PDS) – distance of an individual from principal components curve derived from HCs.
We induced experimental autoimmune encephalomyelitis (EAE) in 7-8 week old C57/BL6 mice (immunization with MOG35-55). At onset of paralysis, we treated mice with oral TUDCA (500 mg/kg) or vehicle till day 28 post-immunization. We also examined effects of TUDCA on polarization of microglia (M1) and astrocytes (A1) *in vitro*.
Results:
In the discovery cohort, MS patients had lower levels of multiple BAs compared to HC. PDS scores were higher in RRMS for secondary BA metabolism ($p=0.002$) while PMS had abnormalities in both primary and secondary BA metabolism ($p<0.002$ for both). In the validation cohort, PDS scores for primary ($p<0.001$) and secondary ($p=0.027$) BA metabolism were higher in PMS compared to control. In pediatric MS, we again noted higher PDS scores for primary BA metabolism ($p=0.015$).
TUDCA treatment reduced EAE severity ($p=0.01$) and decreased demyelination, immune cell infiltration and astrocytosis. *In vitro* experiments revealed reduction in M1 polarization with TUDCA treatment. In astrocyte cultures with addition of factors (IL-1a, TNF-a, C1q) promoting A1 polarization, TUDCA treatment reduced expression of A1-specific gene transcripts.
Conclusions:
BA metabolism was altered in both adult and pediatric MS. BA supplementation ameliorated EAE and *in vitro* treatment prevented pro-inflammatory polarization of microglia and astrocytes.