Binge Alcohol Consumption in Murine Models of Multiple Sclerosis Leads to Sex-Specific Disease Development

TEXAS
The University of Texas at Austin

Sam Bazzi, Blaine Caslin, Marissa Raskin, Aditi Karmakar, Kailey Mohler, Cole Maguire, Esther Melamed
Department of Neuroscience, The University of Texas at Austin

Introduction

- Although the etiology of multiple sclerosis (MS) remains unknown, up to 70% of the risk is thought to be due to environmental factors.
- One largely understudied risk factor in MS is diet, including alcohol consumption. Because alcohol consumption is a modifiable lifestyle factor with immunological and neurological effects, it is important to understand its role in MS, especially given the high comorbidity between MS and alcohol use disorder.
- Our previous work demonstrated that low, chronic alcohol intake (2.6% ABV) in a mouse model of MS – MOG_{35-55}-induced experimental autoimmune encephalomyelitis (EAE) – caused significantly greater remission of disease in males compared to females.

Objectives and Methods

- Our objective in this study was to assess how high doses of alcohol may affect the onset and progression of disease in EAE.
- We utilized two models of EAE, MOG_{35-55} inducible model in C57BL/6 mice and 2D2 spontaneous EAE mouse model.
- In the C57BL/6 inducible EAE model, we administered a high dose of alcohol via oral gavage (3.5g/kg or control) three times per week for three weeks preceding induction of EAE and continued for 40 days post-induction. Clinical EAE scores were assessed daily starting on day 5 post-EAE induction.
- In the spontaneous 2D2 model, adult 2D2 mice were fed a daily Lieber-DeCarli liquid diet containing alcohol (6% v/v or control). Blood alcohol concentrations and daily caloric intake were assessed in the gavage and liquid diet model, respectively.

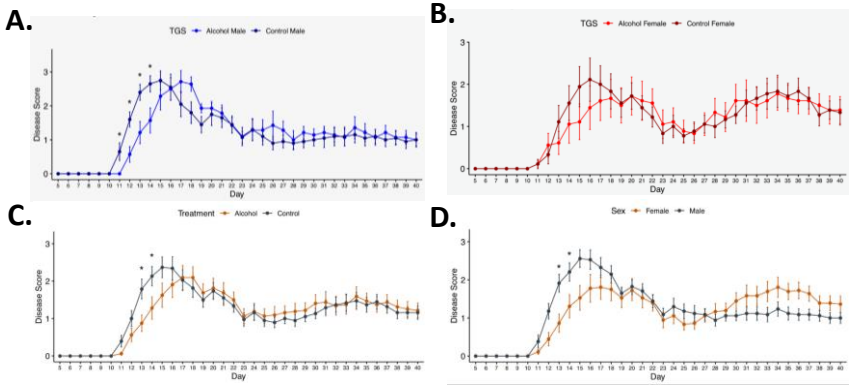
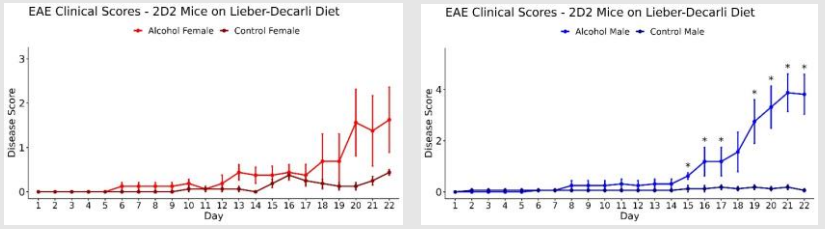


Figure 1. High dose alcohol (3.5 g/kg, 3x per week) delayed the onset of MOG_{35-55}-induced EAE in males, but not females. In the C57BL/6 inducible MOG_{35-55} model, we observed that high dose of alcohol delayed the onset of disease in a sex-specific manner, with alcohol-consuming (AC) males developing delayed clinical EAE score peaks relative to isocaloric controls (panel A) and compared to AC females (panel B). Curves for treatment and sex – panels C and D, respectively. BAC measurements confirmed intoxication in this model, with a mean BAC of 324.7mg/dL (data not known).



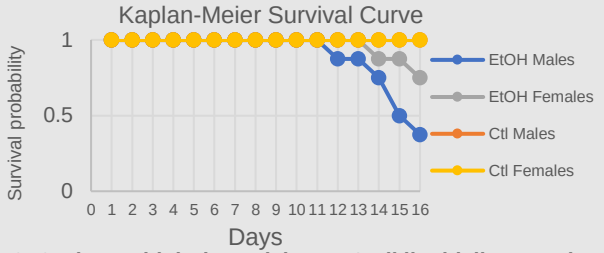


Figure 2. Male 2D2 Mice on high-dose Lieber-DeCarli liquid diet experienced a high death rate. In the 2D2 model, AC males experienced a high death rate starting day 11 post-introduction of the alcohol diet, with a survival probability of AC males by day 16 of 0.375. AC females had a higher survival probability of 0.75 by day 16.

Results

- High dose alcohol delayed the onset of inducible EAE in males but not females.
- High dose alcohol in 2D2 mice was associated with high mortality, specifically in males. The experiment was ended on day 16 for this reason.
- During the final week of the experiment, the 2D2 mice exhibited shaking behavior upon handling.

EAE Score	Description
0	No disability
1	Limp tail
2	Limp tail + hind limb weakness
3	Limp tail + hind limb paralysis
4	Previous + front limb weakness
5	Moribund

Future Directions

- Evaluate dose-dependent relationship between alcohol and neuroinflammation to test the hypothesis that high dose alcohol has deleterious effects on EAE onset and development.
- Determine cause of neurological symptoms (shaking) and conduct histology on brain sections in 2D2 mice treated with high dose alcohol.
- Determine if mortality in 2D2 mice was caused by alcohol toxicity vs autoimmune demyelination due to MOG-reactive T-cells inherent in 2D2 mice.

Acknowledgements: We would like to thank Bob Messing, Linda Noble, Andrew Gaudet, and Todd Triplett for their support and guidance

Funding: T32 AA007471, Bruce/Jones Graduate Fellowship, Dell Medical School Startup, K08 26-1616-11