Elevated Interleukin-6 Activity is Associated with Adrenal Insufficiency in Outpatients with Decompensated Cirrhosis

Calvin X. Geng, MD[1]; Brian J. Wentworth, MD[2]; Helmy Siragy, MD[3]; Zachary H. Henry, MD[2]

Department of Medicine, University of Virginia Medical Center, Charlottesville, VA[1]

Division of Gastroenterology & Hepatology, University of Virginia Medical Center, Charlottesville, VA[2]

Division of Endocrinology and Metabolism, University of Virginia Medical Center, Charlottesville, VA[3]

BACKGROUND

- Adrenal insufficiency (AI) is common in patients with decompensated cirrhosis and associated with increased mortality[1,2], however its pathophysiology is incompletely understood.
- AI in cirrhosis has primarily been studied in hospitalized patients whose hypothalamic-pituitary-adrenal axis functionality is confounded by acute illness[3,4].
- Though cytokine levels are increased in patients with cirrhosis[5], whether a distinct profile characterizes patients with AI remains undefined[3]

STUDY AIMS

- To investigate whether AI in outpatients with decompensated cirrhosis is characterized by a unique cytokine profile
- Elucidate possible pathophysiologic mechanisms underlying AI in decompensated cirrhosis

METHODS

- 34 adult patients with decompensated cirrhosis (Child-Pugh B [CP-B] or C [CP-C]) were prospectively recruited from outpatient clinics.
- 13 cytokines (IL-1a, IL-1b, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-17A, IL-18, IFNγ, TNFa) were assessed using the Luminex Multiplex Immunoassay.
- ACTH levels were collected and standard dose (250µg) cosyntropin stimulation test was administered with AI defined as an increase in total cortisol <9 µg/dL

Table 1: Selected Patient Characteristics by AI Status

	All	Normal adrenal function (n=21)	Adrenal insufficiency (n=13)	P value
N (%)	34	21 (62)	13 (38)	-
Age (y)	59 ± 11	59 ± 12	60 ± 9	0.738
Sex (M/F)	14 (41) / 20 (59)	7 (50) / 7 (50)	3 (27) / 11 (73)	0.477
Δ total cortisol (µg/dL)	10.5 ± 3.2	12.3 ± 2.7	7.5 ± 1.1	< 0.0001
Albumin (g/dL)	3.2 ± 0.6	3.3 ± 0.6	3.1 ± 0.6	0.369
ACTH		13 (10, 23)	16 (9, 22)	1.000
Etiology (%)				1.000
Alcohol	9 (26)	6 (29)	3 (23)	
NASH	13 (38)	8 (38)	5 (38)	
Mixed	4 (12)	2 (10)	2 (15)	
Other	8 (24)	5 (24)	3 (23)	
Child-Pugh score (IQR)	8 (7,9)	8 (7,9)	8 (8,10)	0.360
Child-Pugh class B (%) / C (%)	26 (76) / 8 (23)	17 (81) / 4 (19)	9 (69) / 4 (31)	0.680
MELD (IQR)	12 (9,15)	11 (8, 14)	13 (11,15)	0.094

Values reported as mean (SD) or median (IQR) based on normality of sampling distribution for each variable

Table 2: Cytokine Analysis

	Normal adrenal function (n = 21)	Adrenal insufficiency (n = 13)	P value
IL-1a (pg/mL)	4.56 (4.51, 17.02)	4.51 (4.51, 15.46)	0.771
IL-1b (pg/mL)	38.75 (12.05, 95.52)	29.75 (10.05, 58.97)	0.645
IL-1RA (pg/mL)	18.43 (13.70, 30.59)	14.16 (8.6, 21.05)	0.357
IL-2 (pg/mL)	5.34 (0.62, 21.53)	5.20 (0.74, 18.48)	0.800
IL-4 (pg/mL)	0.28 (0.28, 7.33)	0.28 (0.28, 4.75)	0.897
IL-5 (pg/mL)	2.89 (1.48, 15.69)	4.55 (2.14, 7.11)	0.954
IL-6 (pg/mL)	**12.29 (5.47, 23.57)**	**24.12 (15.10, 38.91)**	**0.046**
IL-8 (pg/mL)	49.65 (28.24, 81.67)	33.35 (27.51, 60.68)	0.466
IL-10 (pg/mL)	14.91 (8.28, 36.56)	24.64 (13.64, 35.34)	0.378
IL-17A (pg/mL)	10.74 (2.04, 52.78)	5.29 (0.43, 33.00)	0.817
IL-18 (pg/mL)	34.86 (27.71, 69.14)	34.50 (16.01, 57.58)	0.848
IFNγ (pg/mL)	10.78 (1.62, 33.71)	12.43 (2.59, 30.89)	0.659
TNFa (pg/mL)	37.14 (13.94, 108.75)	33.66 (17.25, 69.97)	0.759

Values reported as mean (SD) or median (IQR) based on normality of sampling distribution for each variable

RESULTS

- Interim analysis on 34 patients revealed a median MELD of 12, with 26 CP-B and 8 CP-C.
- Thirteen participants (38%) met AI criteria; 50% of all CP-C participants (n=4) had RAI vs. 35% of all CP-B (n=9) participants
- Baseline characteristics between AI and non-AI groups with respect to disease etiology and severity were similar, as were ACTH levels
- Cytokine analysis revealed no significant differences in levels of pro- and anti-inflammatory (IL-1RA, IL-4, IL-10) cytokines between groups with the exception of IL-6 levels being higher in patients with AI ($p < 0.05$).

CONCLUSIONS

- In this hypothesis-generating study, elevated interleukin-6 levels were associated with the presence of AI in decompensated cirrhosis.
- Outside of IL-6, cytokine levels were similar between AI and non-AI outpatients with decompensated cirrhosis, arguing against global immune dysregulation as a significant mechanism underlying AI in cirrhosis.
- Whether elevated IL-6 levels suppress ACTH release or whether IL-6 is increased given low total cortisol levels is unclear and is an important avenue for further research.

Contact

Calvin X. Geng – PGY-2, Internal Medicine

Phone: 512-633-0810

Email: MUH7ZJ@virginia.edu

Twitter: @CalvinGeng

References

1. Wentworth BJ, Siragy HM. Adrenal Insufficiency in Cirrhosis. J Endocr Soc. 2022 Jul 29;6(10):bvac115. doi: 10.1210/jendso/bvac115. PMID: 36033971;
2. Kim G, Huh JH, et al. Relative Adrenal Insufficiency in Patients with Cirrhosis: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2017 Apr;62(4):1067-1079. doi: 10.1007/s10620-017-4471-8. Epub 2017 Feb 7. PMID: 28176190.
3. Acevedo J, Fernández J, et al. Relative adrenal insufficiency in decompensated cirrhosis: Relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. Hepatology. 2013 Nov;58(5):1757-65. doi: 10.1002/hep.26535. Epub 2013 Aug 7. Erratum in: Hepatology. 2015 Jun;61(6):2121. PMID: 23728792.
4. Triantos CK, Marzigie M, et al. Critical illness-related corticosteroid insufficiency in patients with cirrhosis and variceal bleeding. Clin Gastroenterol Hepatol. 2011 Jul;9(7):595-601. doi: 10.1016/j.cgh.2011.03.033. PMID: 21545846.
5. Dirchwolf M, Podhorzer A, et al. Immune dysfunction in cirrhosis: Distinct cytokines phenotypes according to cirrhosis severity. Cytokine. 2016 Jan;77:14-25. doi: 10.1016/j.cyto.2015.10.006. PMID: 26517154.