The Interaction between Inflammatory Genotype and Complicated Grief Disorder Is Associated with Elevated Circulating Levels of IL-6

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Background

- Spousal bereavement is associated with increased morbidity and mortality in the surviving spouse. Although most widow(er)s are resilient, a minority experience a chronic debilitating condition called Complicated Grief disorder[1], showing increased morbidity rates[2].
- However, the mechanism linking Complicated Grief disorder and adverse health outcomes has not been clarified.
- Prior research has identified a G x E interaction between a variation in an inflammatory genotype (*IL-6*) and bereavement on circulating levels of inflammation[3] (Figure 1).
- Genetic variability may interact with Complicated Grief disorder in the expression of inflammatory markers.

Methods

- Sixty-four older adults were recruited from the Los Angeles area (widowed = 36; married/partnered = 28) with an average time since spousal loss of 2 years.
- Inventory of Complicated Grief-Revised (ICG-R)[4]
  - 19 items; assesses indicators of pathological grief, such as anger, disbelief, and hallucinations, on a 5-point scale.
- The Complicated Grief group was determined by a score of 30 or higher on the ICG-R.
- Genomic DNA was extracted from peripheral blood monocytes, and the *IL-6* -174 SNP was determined for each participant.
- Genotype frequencies met Hardy–Weinberg equilibrium and were consistent with the literature.
- High sensitivity ELISA for circulating levels of IL-6 was performed on plasma.

Objective

- The present study compared Complicated Grief, Non-Complicated Grief, and Non-Bereaved married/partnered older adults to examine whether a single nucleotide polymorphism (SNP) in the human *IL-6* gene promoter region (rs1800795 G/C) might influence vulnerability for increased inflammation following spousal loss.

Genotype Frequencies

	Non-bereaved (N=28)		Non-Complicated Grief (n = 23)		Complicated Grief (n= 13)		X^2	P-value
	N	%	N	%	N	%		
IL-6 -174GG (high)	**13**	**46%**	**12**	**52%**	**7**	**54%**	0.26	0.88
IL-6 -174C Carriers (low)	**15**	**54%**	**11**	**47%**	**6**	**46%**		
IL-6 -174CG	11	39%	10	44%	4	31%		
IL-6 -174CC	4	14%	1	4%	2	15%		

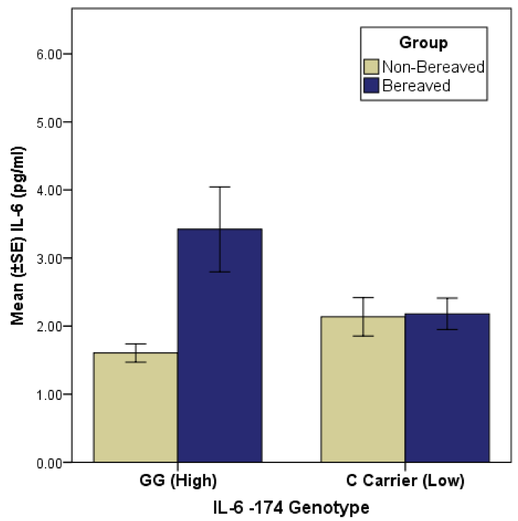
Demographics

	Non-bereaved (n=28)		Non-Complicated Grief (n=23)		Complicated Grief (n=13)		F-value / X^2	P-value
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%		
Age	72.39	4.15	72.83	6.01	73.08	5.52	0.91	0.91
Gender (Female)	15	54%	13	57%	10	77%	2.13	0.35
Ethnicity (non-Caucasian)	5	18%	5	22%	5	39%	2.16	0.34
Employment (Retired)	15	54%	15	65%	8	62%	8.88	0.18
Education (Post graduate)	13	46%	9	39%	5	39%	0.37	0.83
Years married/partnered	41.18	11.24	31.66	18.22	42.69	14.67	3.36	0.41
Body mass index	27.35	5.63	27.01	5.61	25.89	4.66	0.33	0.73
Alcohol (Drinks per week)	1.70	2.89	2.22	4.46	1.87	4.11	0.13	0.88

Continuous variables: mean (±SD), F value (ANOVA); categorical variables: n (%), X^2 value (Chi Square Test).

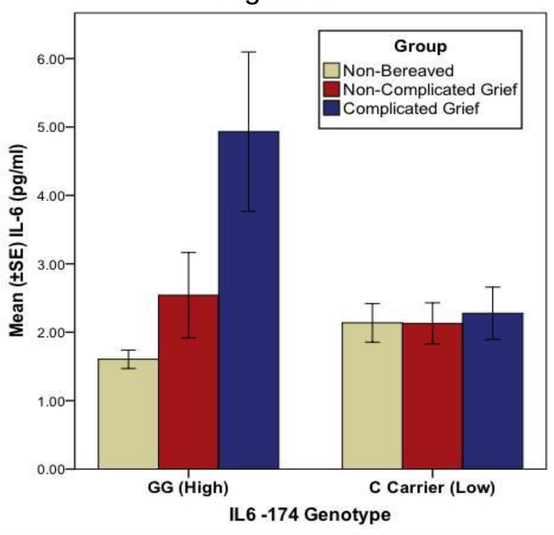
G x E Interaction (Bereavement)[3]

Figure 1



G x E Interaction (CG diagnosis)

Figure 2



Results

- There was a dose-dependent increase in circulating levels of IL-6 across the three groups (NB: 1.9 ± 0.9 pg/ml; NCG: 2.3 ± 1.7 pg/ml; and CG: 3.7± 2.7 pg/ml).
- In a regression controlling for age and BMI, group (β = 0.61) and group x genotype (β = -0.44) were both predictive of circulating IL-6 [F(5,57) = 3.58, p = 0.007].
- All *IL-6* -174 C allele carriers had similar levels of circulating IL-6.
- However, levels of circulating IL-6 were twice as high in Complicated Grief *IL-6* -174 G homozygotes compared to Non-Complicated Grief and Non-bereaved *IL-6* -174 G homozygotes (Figure 2).

Conclusion

- The present study found elevated levels of IL-6 in the Complicated Grief group, explained by the interaction between *IL*-6 -174 SNP and Complicated Grief disorder such that Complicated Grief G homozygotes showed a two-fold increase in IL-6 compared to Complicated Grief C allele carriers.
- The results suggest a possible mechanism for increased morbidity and mortality in widow(er)s suffering from Complicated Grief.
- With future replication, these data might indicate clinical follow up for this group.

References

1. Shear, M. K., Simon, N., Wall, M., Zisook, S., Neimeyer, R., Duan, N., . . . First, M. (2011). Complicated grief and related bereavement issues for DSM-5. *Depression & Anxiety (1091-4269), 28*(2), 103-117. doi:10.1002/da.207802.
2. Prigerson, H. G., Maciejewski, P. K., Reynolds III, C. F., Bierhals, A. J., Newsom, J. T., Fasiczka, A., . . . Miller, M. (1995). Inventory of complicated grief: A scale to measure maladaptive symptoms of loss. *Psychiatry Research, 59*(1–2), 65-79. doi:10.1016/0165-1781(95)02757-2
3. Schultze-Florey, C. R., Martínez-Maza, O., Magpantay, L., Breen, E. C., Irwin, M. R., Gündel, H., & O'Connor, M. F. (2012). When grief makes you sick: Bereavement induced systemic inflammation is a question of genotype. *Brain, behavior, and immunity*, *26*(7), 1066-1071. doi:10.1016/j.bbi.2012.06.009
4. Prigerson, H. G., Bierhals, A. J., Kasl, S. V., Reynolds, C., Shear, M. K., Day, N., . . . Jacobs, S. (1997). Traumatic grief as a risk factor for mental and physical morbidity. *American Journal of Psychiatry, 154*, 616-623.

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