Breakdown of the Gut Paracellular and Blood-brain Barrier are Risk Factors of Delirium due to Hip Fracture in Older Adults

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INTRODUCTION

Delirium is accompanied by immune-inflammatory response system activation, which may cause breakdown of the blood-brain-barrier (BBB) and may be induced by gut barrier disruption. Some results suggest that the BBB is compromised in delirium, but there is no data regarding the gut barrier.

This study investigates whether delirium is associated with impaired BBB and gut barriers in elderly adults undergoing hip fracture surgery.

METHODS

We recruited 59 older adults and measured peak Delirium Rating Scale (DRS) scores 2-3 days after surgery, and assessed plasma IgG/IgA levels (using ELISA techniques) for zonulin, occludin, claudin-6, β-catenin, actin (indicating damage to the gut paracellular pathway), claudin-5 and S100B (reflecting BBB damage), lipopolysaccharides (LPS), LPS-binding protein (LBP); bacterial cytolethal distending toxin (CDT), *P. gingivalis*, and *H. pylori*).

RESULTS

Results from univariate analyses showed that delirium is linked to increased IgA responses to all of the self-epitopes and antigens listed above, except for LPS. Increased IgA reactivity to the paracellular pathway and BBB proteins, and bacterial antigens is significantly associated with activation of M1 macrophage, T helper-1 and 17 cytokine profiles.

Table 1. Socio-demographic, clinical and immune data in older adults divided into those with lower and higher peak Delirium Rating Scale, (DRS) scores on days 2 and 3 after surgery (peak DRS).

Variables	Low peak DRS (N=36)	High peak DRS (N=23)	F/χ2	df	P
DRS day0	2.28 (2.42)	3.48 (2.50)	3.36	1/57	0.072
DRS day1	1.86 (1.94)	4.87 (3.98)	15.06	1/57	<0.001
Peak DRS day2+3	2.15 (0.95)	6.78 (2.54)	54.69	1/57	<0.001
Age (years)	77.9 (7.7)	85.0 (5.9)	13.89	1/57	<0.001
Sex (F/M)	28/8	18/5	0.00	1	0.965
Education (years)	8.3 (5.4)	7.7 (6.4)	0.18	1/57	0.676
Body mass index (kg/m2)	22.02 (3.13)	21.51 (3.34)	0.33	1/57	0.567
Fall to hospital (hours)	2.2 (4.9)	1.3 (1.1)	0.61	1/57	0.439
Hospital to surgery (hours)	74.4 (76.2)	74.1 (58.5)	0.00	1/57	0.989
Length of stay (days)	9.2 (4.4)	12.1 (6.4)	4.29	1/57	0.043
Insomnia (0/1/2)	10/11/9	3/7/11	3.37	2	0.187
Blood loss (mL)	210.0 (115.6)	201.3 (107.0)	0.08	1/57	0.773
IRS (z scores)	-0.255 (0.938)	0.424 (1.071)	6.50	1/57	0.013
CIRS (z scores)	0.0423 (0.927)	0.838 (1.064)	0.03	1/57	0.876
IRS/CIRS (z scores)	-0.258 (0.913)	0.392 (0.966)	6.69	1/57	0.012

Table 2. Results of generalized estimating equations (GEE) with the Delirium Rating Scale (DRS), continuous score as dependent variables, and IgA responses to self-antigens as explanatory variables.

Peak DRS2+3 (GEE)	B	SE	Lower 95% CI	Higher 95% CI	Wald (df=1)	p
IgA Bacterial	1.271	0.3862	0.514	2.028	10.83	<0.001
IgA Tight junctions	1.303	0.3911	0.536	2.069	11.09	<0.001
IgA Blood brain barrier	1.297	0.3962	0.521	2.073	10.72	0.001
IgA β-catenin-actin	1.314	0.3954	0.539	2.089	11.05	<0.001
IgA LPS-LPB	1.197	0.3942	0.425	1.970	9.22	0.002
IgA LPS	0.819	0.4310	-0.026	1.664	3.61	0.057
IgA LPB	1.219	0.3445	0.544	1.894	12.52	<0.001
IgA Zonulin	1.027	0.4146	0.214	1.839	6.14	0.013
IgA Occludin	1.245	0.3883	0.484	2.006	10.28	0.001
IgA Claudin-5	1.325	0.3822	0.576	2.074	12.02	<0.001
IgA Claudin-6	1.315	0.3867	0.557	2.073	11.56	<0.001
IgA S100B	1.178	0.4006	0.393	1.963	8.65	0.003
IgA β-catenin	1.255	0.3846	0.501	2.009	10.65	0.001
IgA Actin	1.203	0.3855	0.447	1.958	9.73	0.002
IgA CDT	1.304	0.4025	0.515	2.093	10.50	0.001
IgA *P. gingivalis*	1.145	0.4133	0.335	1.955	7.67	0.006
IgA *H. pylori*	1.221	0.4055	0.426	2.015	9.06	0.003

Discussions

Delirium and DRS scores are predicted by IgA responses to bacterial, LPS-LBP, TJ, BBB breakdown, and β-catenin-actin (CATACT) complex in older adults with hip fractures. To our knowledge, this is the first study demonstrating an association between delirium severity and IgA responses to LPS, LPB, CDT, *H. pylori*, *P. gingivalis*, zonulin, occludin, claudin-5, claudin-6, β-catenin, and actin.

These IgA findings imply leaky gut, namely the breakdown of TJs and AJs and increased translocation of common Gram-negative or Gram-positive microbiota or their detrimental antigens into the systemic circulation.

The delirious patients in our study also showed significantly increased IgA reactivity to S100B, and claudin-5, which are specific products of BBB breakdown.

Moreover, immune-inflammatory response system (IRS) activation (increased M1 [with IL-1β, IL-6, IL-8 and TNF-α], Th1, Th17, and T cell growth profiles) in the postoperative period is strongly associated with IgA responses to paracellular and BBB composites and bacterial antigens. Our results indicate that leaky barriers and bacterial antigens increase the risk of delirium in part by activating the IRS.

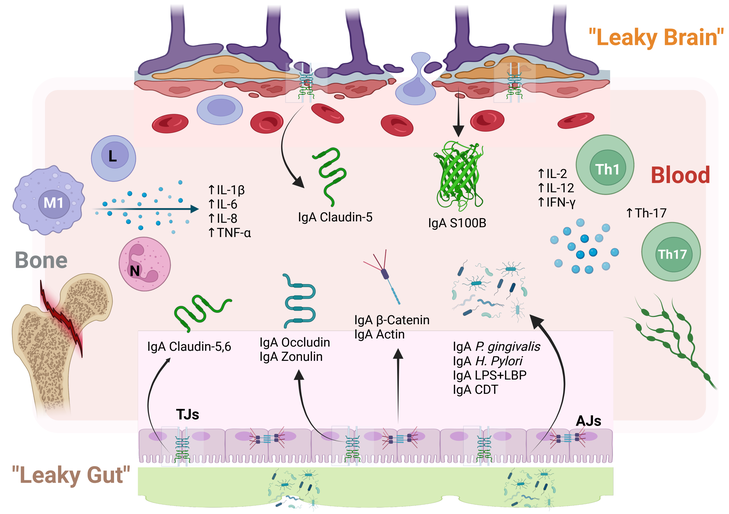

Figure 1. Older adults with hip fracture, systemic immune-inflammatory response activation, gut barrier damage, bacterial translocation, blood brain barrier disruption, and delirium.

A limitation of this study could be the smaller sample size of older adults with hip fractures. Nevertheless, the a priori estimated sample size was at least 49. All statistical regressions controlling for age indicate that age and IgA levels affect delirium symptoms independently. An open question is whether these biomarkers are trait (risk factors of post-injury delirium) or state biomarkers of delirium. Therefore, future research should measure these biomarkers before trauma and surgery and again after surgery.

Conclusions

Aberrations in the tight and adherens junctions of the gut and BBB barriers, leaky gut with bacterial translocation, elevated CDT and LPS load in peripheral blood are risk factors for delirium.

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