Examining the metabolite relationships across the blood-brain barrier (BBB) and their associations with postoperative delirium

Mijin Jung[1], Xiaobei Pan[1], Emma L. Cunningham[2], Aoife Sweeney[2], Anthony P. Passmore[2], Bernadette McGuinness[2], Daniel F. McAuley[3], David Beverland[4], Seamus O'Brien[5], Tim Mawhinney[5], Brian D. Green[1]*

1. Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, 8 Malone Road, Belfast, BT9 5BN, Northern Ireland, UK
2. Centre for Public Health, Queen's University Belfast, Block B, Institute of Clinical Sciences, Royal Victoria Hospital site, Grosvenor Road, Belfast, BT12 6BA, Northern Ireland, UK
3. Centre for Experimental Medicine, Queen's University Belfast, Wellcome-Wolfson Institute for Experimental Medicine, 97 Lisburn Road, Belfast, BT9 7BL, Northern Ireland, UK
4. Outcomes Assessment Unit, Musgrave Park Hospital, Belfast Trust, Stockman's Lane, Belfast, BT9 7JB, Northern Ireland, UK
5. Cardiac Surgical Intensive Care Unit, Belfast Trust, Royal Victoria Hospital, Grosvenor Road, Belfast, BT12 6BA, Northern Ireland, UK

QUEEN'S UNIVERSITY BELFAST EST⅌1845

INTRODUCTION

- Blood-brain barrier (BBB) disruption has been suggested as a risk factor for delirium.
- Studies have also found changes in either cerebrospinal fluid (CSF) or blood metabolites associated with delirium.
- This investigation examined whether metabolite relationships across the BBB are linked to delirium.

MATERIALS & METHODS

1. Participants recruitment

(1) Surgery: Knee or hip surgery
(2) Age: over 65 years
(3) Incident of delirium: 44/315 (14.0%)
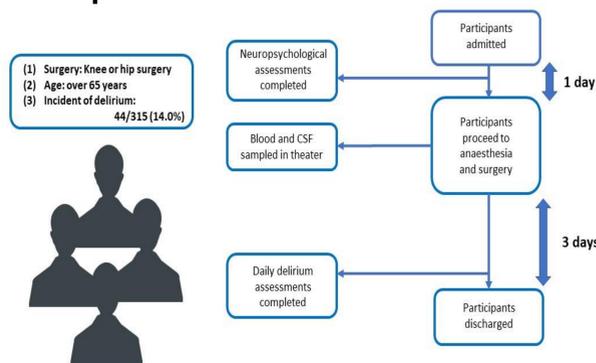
- Participants (*n* = 54) matched for age and gender were sampled from an observational cohort study of people ≥65 years without a diagnosis of dementia presenting for primary elective hip or knee arthroplasty.

2. Sample collection

N= 54   Plasma   CSF
Preoperatively collected
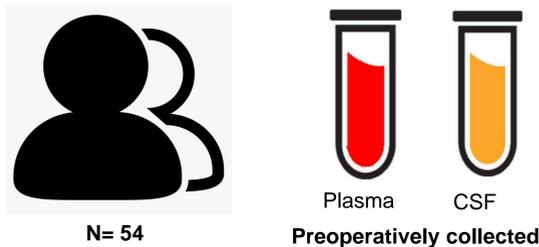
- Plasma and CSF samples were collected pre-operatively.
- Groups: control (*n* = 26, aged: 75.8 ± 5.2) and delirium (*n* = 28, aged: 76.2 ± 5.7).
- CSF and plasma albumin were measured using the Roche cobas immunoturbidimetric assay and the CSF/plasma ratio (Qalb) was calculated

3. Targeted metabolomics

Xevo TQ-S
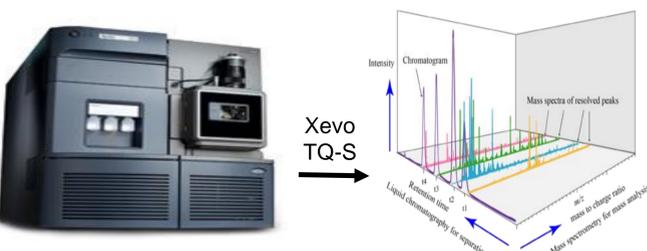
- Metabolite profiling of plasma and CSF was undertaken using a triple-quadrupole mass spectrometer.

4. Data analysis

- **Statistics**
Student's t-test
Mann-Whitney U test
X2: Chi-square test
False discovery rates(FDR, q-value)

- **Figures**
Prism8 (Software)
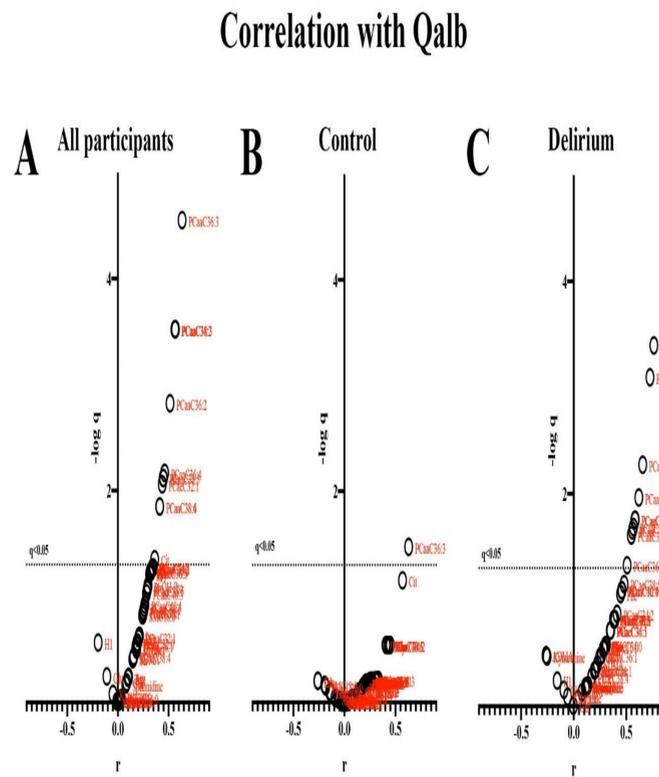
Prism 8

RESULTS

Correlation with Qalb

Fig 1. Correlation of Qmetab with Qalb. (A) The correlation curve between Qalb and Qmetab in all participants. (B) The correlation curve between Qalb and Qmetab in control. (C) The correlation curve between Qalb and Qmetab in delirium. The X-axis represents the correlation coefficient r-value from spearman r and the y-axis represents –log q, and values above the dotted line indicate a q-value lesser than 0.05.
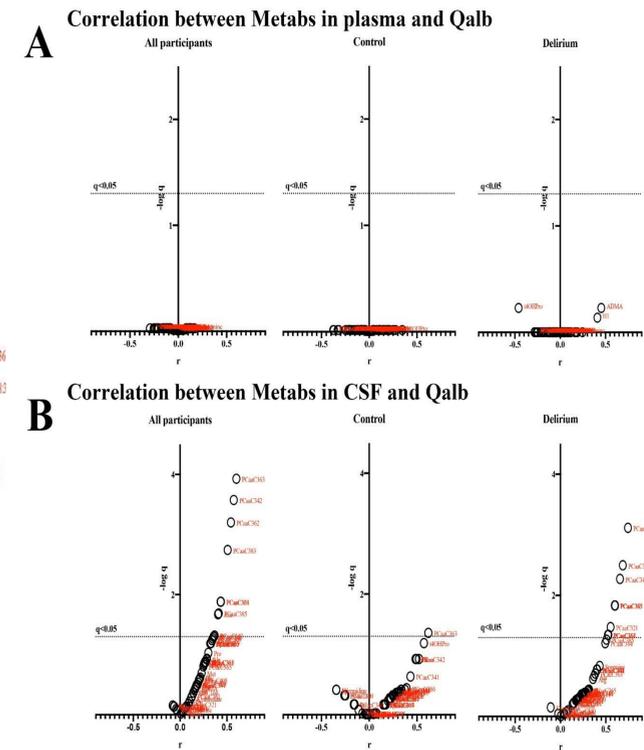
Fig 2. Correlation of plasma and CSF metabs with Qalb. (A) The correlation curve between plasma metabs and Qalb in all participants, control, and delirium (B) The correlation curve between CSF metabs in CSF and Qalb in all participants, control, and delirium. The X-axis represents the correlation coefficient r-value from spearman r and the y-axis represents –log q, and values above the dotted line indicate a q-value lesser than 0.05.

Metabolite	Control (plasma) Mean±SD(g/L)	Delirium (plasma) Mean±SD(g/L)	↑↓	% difference	Control (CSF) Mean±SD(mg/L)	Delirium (CSF) Mean±SD(mg/L)	↑↓	% difference
PC aa C34:1	224.1 ± 56.52	217.5 ± 59.13	↓	-2.95	1.924 ± 0.471	2.003 ± 0.567	↑	4.11
PC aa C34:2	332.2 ± 99.46	296.1 ± 60.02	↓	-10.87	0.180 ± 0.051	0.210 ± 0.147	↑	16.41
PC aa C36:2	179.0 ± 46.17	167.8 ± 29.81	↓	-6.22	0.183 ± 0.065	0.213 ± 0.116	↑	16.36
PC aa C36:3	108.2 ± 29.04	101.2 ± 18.72	↓	-6.47	0.067 ± 0.028	0.087 ± 0.062	↑	30.58
PC aa C36:4	171.0 ± 56.17	163.8 ± 42.82	↓	-4.21	0.181 ± 0.058	0.226 ± 0.154	↑	24.86
PC aa C38:3	43.17 ± 12.70	39.98 ± 8.68	↓	-7.39	0.049 ± 0.024	0.058 ± 0.028	↑	18.03
PC aa C38:4	90.27 ± 29.84	86.75 ± 24.43	↓	-3.90	0.172 ±0.052	0.201 ± 0.112	↑	16.49
PC aa C38:5	46.83 ± 13.20	45.29 ± 12.38	↓	-3.29	0.048 ± 0.019	0.056 ± 0.031	↑	16.67
PC ae C32:1	2.333 ± 0.641	2.344 ± 0.550	≈	0.47	0.018 ± 0.009	0.020 ± 0.013	↑	14.04
PC ae C34:2	7.223 ± 2.352	6.841 ± 1.746	↓	-5.28	0.033 ± 0.014	0.046 ± 0.026	↑	39.07
PC ae C36:2	9.617 ± 2.613	9.844 ± 2.548	↑	2.36	0.019 ± 0.010	0.020 ± 0.013	↑	5.15

Table 1. Comparison of metabolite concentration of glycerophospholipids between control and delirium in both plasma and CSF. CSF: cerebrospinal fluids, SD: standard deviation.

CONCLUSION

- The CSF/plasma ratios of several phospholipids correlate with Qalb in delirium, but not control, groups.
- The BBB is a highly selective permeable cellular phospholipid protein bilayer barrier.
- This suggests that in people prone to delirium, which could be a proxy for neurodegeneration, CSF concentrations of phospholipids, relative to plasma levels, increase more in line with increasing BBB permeability than happens in people with no delirium.
- What this means for the processes of neurodegeneration that likely increase delirium susceptibility, and also the pathophysiological processes that lead directly to delirium, require further evaluation.

REFERENCES

1) Knox EG, Aburto MR, Clarke G, Cryan JF, O'Driscoll CM. (2022). The blood-brain barrier in aging and neurodegeneration. Mol Psychiatry. 27(6):2659-2673.
2) Kosicek M, Hecimovic S. (2013). Phospholipids and Alzheimer's disease: alterations, mechanisms and potential biomarkers. Int J Mol Sci. 14(1):1310-22.

Trauma & Orthopaedics Research Charity