CCL2 and CXCL2 are Markers of Delirium Vulnerability in Community Dwelling Older People

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Immune Ageing, Senescence and Frailty	
IL-6	Pro-inflammatory cytokine. Raised in inflammaging.
IL-10	Anti-inflammatory cytokine. Involved in inflammageing.
CCL4/MIP1β	Involved in the recruitment and activation of cells expressing CCR2 or CCR5 including granulocytes, t lymphocytes and NK cells. Indicated as a marker for frailty/sarcopenia.
MIF	Regulates macrophages through suppressing the anti-inflammatory effects of glucocorticoids. Indicated as a marker for frailty/sarcopenia.
CXCL9/MIG	Released by several cells in response to IFN-γ. Particularly important in the chemoattraction of T-lymphocytes of the TH-1 phenotype. Marker of epigenetic age.
GDF-15 /MIC-1	Member of the TGFβ superfamily. Indicated as a marker of frailty/sarcopenia
Osteopontin/ OPN	Matricellular protein that mediates diverse biological functions. Indicated as a marker of frailty/sarcopenia.
CXCL1	Chemoattractant for a number of cells, especially neutrophils. Marker of immune ageing.
Monocyte activation, migration, adhesion and activity or BBB dysfunction	
IL-8	Chemokine produced by macrophages that leads to neutrophil recruitment.
CCL2/ MCP-1	Chemokine that attracts monocytes to site of inflammation
CX3CL1/ Fractalkine	Potently chemoattracts T cells and monocytes. Essential for microglial migration.
e-selectin	Cell adhesion molecule important in recruitment of leukocytes
p-selectin	Cell adhesion molecule important in recruitment of leukocytes
PECAM-1 /CD31	Marker of BBB breakdown. Important in monocyte transmigration.
CXCL2	Secreted by monocytes/macrophages and attracts neutrophils
GM-CSF	Promotes proliferation of granulocytes and monocytes
CD163	Marker of cells of the monocyte/macrophage lineage. Soluble form upregulated in a number of inflammatory conditions.
S100β	Marker of BBB dysfunction
NSE	Marker of BBB breakdown
MMP-3	Marker of BBB dysfunction
Identified as possible biomarker for risk of delirium from literature review	
IL2	Secreted by CD4+ and CD8+ T cells and promotes T cell differentiation and enhances the killing abilities of NK cells and CD8+ T cells. Evidence of higher level in those at risk of delirium.

TABLE 1 Description of Analytes included in the Multiplex Panel

BACKGROUND

Delirium affects one in five older people in hospital, and leads to increased mortality, dementia, and significant distress. The pathophysiology is complex and currently not well understood. However common triggers such as infection and surgery may activate the peripheral immune system, which in turn leads to neuroinflammation, blood-brain-barrier (BBB) dysfunction and neuronal injury(1). Older age is a risk factor for delirium and the immune system changes with age(2). Markers of accelerated immune ageing may therefore explain vulnerability to delirium.

OBJECTIVES

To investigate delirium vulnerability by measuring markers of:

1. immune cell activation, adhesion and migration
2. accelerated immune ageing
3. BBB dysfunction

at baseline in older people that had one or more episodes of delirium over a 2-year follow-up period, compared to those that had no delirium episodes.

LABORATORY METHODS

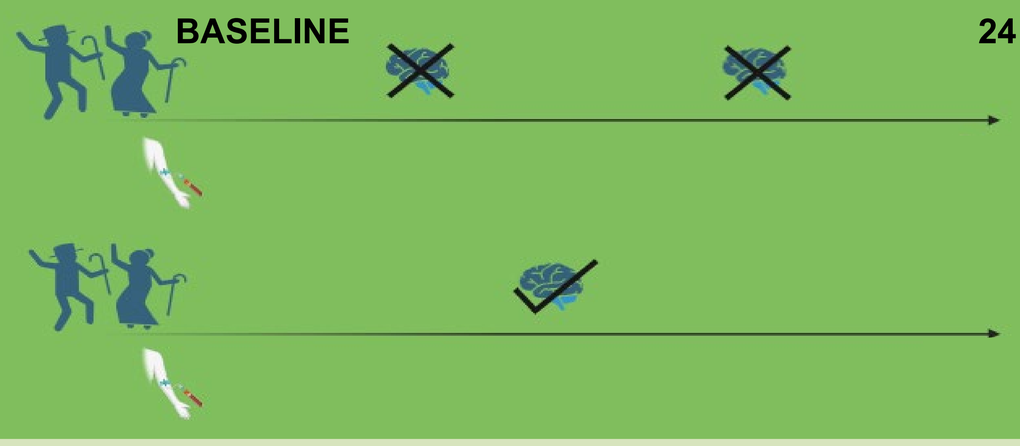
Whole blood was centrifuged, and serum stored at -80^{o}C. Multiple analytes were measured using a multiplex panel.

STATISTICAL ANALYSIS

Data was non-parametric and Mann-Whitney U test was used to compare groups

STUDY PROCEDURE

Norwegian older people (≥65) receiving domiciliary care services ≥once per week were followed up for 2 years and participants were screened for delirium, weekly or at any hospitalisation. Diagnosis was then confirmed against DSM 5 criteria. Participants who had one or more episode of delirium during the follow up period formed the delirium group. Participants with no episodes formed the no delirium group. Blood was taken at baseline.



RESULTS

Multiplex results were available for 98 participants. The median age of the population was 88 years (SD 10.25) and participants were almost exclusively frail (89.9%). 43 participants (43.9%) had at least one episode of delirium during the 2-year follow up period.

Ten markers had >30% of values below the detection level and results were not analysed further.

CCL2 (MCP-1) was significantly higher in the delirium group compared to the no delirium group (13.38 (6.72) vs. 10.83 (5.61) p=0.04). CXCL2 (MIP-2α) was significantly higher in the delirium group compared to the no delirium group (17.23 (12.42) vs. 13.49 (7.79) p=0.031).

When a logistic regression model was used to control for age and dementia, CCL2 (OR 0.999, 95% CI 0.96201.038) and CXCL2(OR 1.032, 95% CI 0.994-1.071) lost significance.

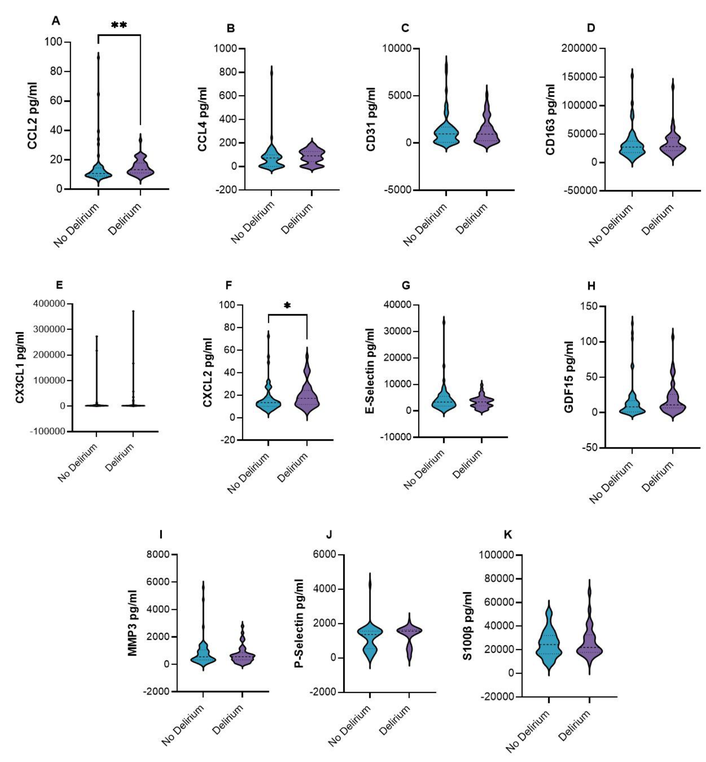


Figure 1 A-K represent the median and IQRof participants who had no episodes of delirium vs. participants who had ≥1 episodes of delirium in the 2-year follow up perdiod. Groups were compared using Mann-Whitney U Test and significance was set at 95%

DISCUSSION

CCL2 and CXCL2 are chemokines involved in immune cell recruitment and markers of accelerated immune ageing.

Previous work has implicated the CCL2/CCR2 axis in delirium pathophysiology(3,5), but this is the first study to link CXCL2 to delirium in humans.

Future work should focus on elucidating the role of immune cell recruitment and brain infiltration in delirium to identify potential treatment targets. . CCL2 and CXCL2 are also markers of accelerated immune ageing(5). This suggests that the development of geroprotective agents that target this, may be protective for delirium.

STRENGHTS/LIMITATIONS

High delirium rates and good delirium capture	Small sample
Understudied population with high levels of frailty	Variable time between blood test and delirium episode
	Variable follow up length due to high mortality

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