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Cerebrospinal fluid interleukin-8 levels are higher in hip fracture patients with peri-operative delirium versus controls

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To the Editor

Delirium is often precipitated by peripheral infection or injury, but the causal pathways remain unclear. One hypothesis is that the central nervous system (CNS) changes resulting in delirium are triggered by peripheral inflammation induced by such insults.^{1,2} Indeed, several studies have linked altered serum inflammatory markers with delirium. Higher serum levels of interleukin (IL)-6 and IL-8 were reported in hip fracture patients with delirium compared to controls,^{3,4} and other studies have reported elevated inflammatory markers such as C-reactive protein and interferon gamma, and reduced anti-inflammatory markers such as insulin-like growth factor 1 and IL-1ra in delirium.^{5,6}

With ageing, particularly where there is neurodegeneration, CNS immune cells show exaggerated production of pro-inflammatory cytokines in response to peripheral stimulation, providing a possible causal pathway from the periphery to CNS dysfunction and consequent delirium.² This has been demonstrated in several animal studies^{1,2} but whether there are elevations in CNS pro-inflammatory cytokines in patients with delirium not caused by primary CNS disorders is unknown.

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Here we compared levels of interleukin (IL)1 β , IL-6, IL-8, IL-10 and IL-12p70, and tumor necrosis factor alpha (TNF- α) in the cerebrospinal fluid (CSF) and serum of older hip fracture patients with and without peri-operative delirium. We hypothesized that cases would have higher levels of pro-inflammatory cytokines.

Thirty-six patients (28 female) in two university-affiliated hospitals (Edinburgh, Scotland and Amsterdam, the Netherlands) aged 62-93 years with hip fracture and awaiting surgery were assessed for delirium before and 3-4 days after surgery. Delirium was assessed with the Confusion Assessment Method; patients with delirium at any stage were considered cases. CSF in all patients, and serum in the 16 Edinburgh patients, were obtained at the onset of spinal anesthesia as previously described.⁷ CSF and serum samples were spun at 1000g for 10 minutes at 4°C; supernatants were stored at -80°C. Cytokine levels were measured with a cytometric bead array immunoassay (Human Inflammatory Cytokine Kit, BD Biosciences) with a detection limit of 20.0 pg/mL; levels below this limit were considered to be zero. Case versus control comparisons were analyzed using the Mann-Whitney U-test. The study was approved by the local ethics committees.

Delirium was diagnosed in 15 patients. Nine had delirium pre-operatively, and seven further patients developed delirium post-operatively; one patient who had pre-operative delirium recovered after surgery. Mean ages and Charlson Comorbidity Index scores did not differ between the cases and controls. A history of dementia (N=7) was associated with a higher incidence of delirium (p=0.008).

Only IL-8 and IL-6 were detected in CSF with levels above the assay detection limit: IL-8 in 33/36 samples, and IL-6 in 3/36 samples (IL-6 levels were not further analyzed). Delirium cases (N=15) had higher CSF IL-8, with median (IQR) of 69.8 pg/mL (47.9 – 125.6) compared with 39.6 pg/mL (28.0 – 64.5) for controls (N=21; Mann-Whitney U=68, p=0.003) (Figure 1). In the 16 serum samples the following cytokines had levels above the detection limit: IL-8 (4/16 samples), IL-6 (12/16 samples) and TNF- α (2/16 samples). Serum IL-8 and TNF- α levels were not further analyzed. Delirium cases had higher serum IL-6 levels, with median (IQR) of 42.4 pg/mL (28.9 – 438.4) compared with 24.3 pg/mL (0 – 217.2) for controls (U=6; p=0.013). Exclusion of the seven patients with dementia did not change the pattern of results, with both CSF IL-8 and serum IL-6 levels remaining significantly higher in patients with delirium. Dementia was not associated with higher levels of CSF IL-8 or serum IL-6 (p>0.10).

The present study suggests the possibility that delirium is associated with increased CNS production of IL-8. Our findings are also consistent with some other studies which have found higher serum IL-6 levels in delirium. IL-8 and its rodent homolog CXCL1 (or CINC-1) are produced systemically but also by astrocytes, microglia, brain endothelial cells and infiltrated neutrophils in response to peripheral injury or infection.⁸ IL-8 and CXCL1 have generally pro-inflammatory actions.⁸ Though peripheral CXCL1 can cross the blood brain barrier, synthesis by *brain* endothelium in response to systemic inflammation is significant.⁹ CNS production of IL-8 is supported by another recent study of hip fracture patients, in which mental status was not assessed, where median CSF IL-8 levels were 63 pg/mL (range 40-115) versus median serum IL-8 levels of 0 pg/mL (range 0-78).¹⁰ Taken

together, these findings suggest that CNS production of IL-8 induced by peripheral inflammatory stimuli may be linked with delirium, but further research is required. Future studies should confirm these results in larger samples and other populations, employ more sensitive assays, examine relationships with other putative CSF biomarkers of delirium,⁷ and investigate the role of other cytokines.

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Figure 1.

‘Cerebrospinal fluid interleukin-8 levels in patients with and without peri-operative delirium’

CSF: cerebrospinal fluid. IL-8: interleukin 8. Units for IL-8 are pg/mL.

N=15 for delirium patients; N=21 for controls. *Statistical test: Mann-Whitney U=68, p=0.003.