REFERENCES

1. AIRT Working Group I tumori in Italia—Rapporto 2006. Milano: Inferenze, 2006.
2. Rex DK, Johnson DA, Anderson JC et al. American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008 (2009). Am J Gastroenterol 2009;104:739–750.
3. Winawer SJ, Zauber AG, Fletcher RH et al. Guidelines for colonoscopy after polypectomy: A consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterology 2006; 130:1872–1885.
4. Tsai HL, Yeh YS, Yu FJ et al. Predicting factors of postoperative relapse in T2-4N0M0 colorectal cancer patients via harvesting a minimum of 12 lymph nodes. Int J Colorectal Dis 2009;24:177–183. Epub October 14, 2008.
5. Tsai HL, Lu CY, Hsieh JS et al. The prognostic significance of total lymph node harvest in patients with T2-4N0M0 colorectal cancer. J Gastrointest Surg 2007;11:660–665.
6. Duck-Woo K, Dae YK, Tae HK et al. Is T Classification still correlated with lymph node status after preoperative chemoradiotherapy for rectal cancer? Cancer 2006;106:1694–1700.
7. Chikao M, Masato K, Yasuhiro I et al. Remodeling of the immunoinflammatory network system in elderly cancer patients: Implication of inflamm-aging and tumor-specific hyperinflammation. Surg Today 2008;38:873–878.
8. Sansoni P, Vescovini R, Fagnoni F et al. The immune system in extreme longevity. Exp Gerontol 2008;43:61–65.
9. Militello V, Trevisan M, Squarzon L et al. Investigation on the presence of polyomavirus, herpesvirus and papillomavirus sequences in colorectal neoplasms and their association with cancer. Int J Cancer 2008;124:2501–2503.
10. Papamichael D, Audisio R, Horiot JC et al. Treatment of the elderly colorectal cancer patient: SIOG expert recommendations. Ann Oncol 2009;20:5–16.

CEREBROSPINAL FLUID INTERLEUKIN-8 LEVELS ARE HIGHER IN PEOPLE WITH HIP FRACTURE WITH PERIOPERATIVE DELIRIUM THAN IN CONTROLS

To the Editor: Peripheral infection or injury often precipitates delirium, but the causal pathways remain unclear. One hypothesis is that peripheral inflammation induced by such harmful events trigger the central nervous system (CNS) changes resulting in delirium.[1,2] Several studies have linked altered serum inflammatory markers with delirium. Higher serum levels of interleukin (IL)-6 and IL-8 were reported in people with hip fracture with delirium than in controls,[3,4] and other studies have reported high levels of inflammatory markers such as C-reactive protein and interferon gamma and low levels of anti-inflammatory markers such as insulin-like growth factor 1 and IL-1ra in delirium.[5,6]

With aging, particularly when there is neurodegeneration, CNS immune cells show exaggerated production of proinflammatory 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 CNS proinflammatory cytokine levels are high in people with delirium not caused by primary CNS disorders is unknown.

Levels of IL-1β, 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 adults with hip fracture with and without perioperative delirium were compared. It was hypothesized that those with delirium would have higher levels of proinflammatory cytokines.

Thirty-six patients (28 female) in two university-affiliated hospitals (Edinburgh, Scotland, and Amsterdam, the Netherlands) aged 62 to 93 with hip fracture and awaiting surgery were assessed for delirium before and 3 to 4 days after surgery. Delirium was assessed using the Confusion Assessment Method; people 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 1,000 g for 10 minutes at 4°C; supernatants were stored at −80°C. Cytokine levels were measured using a cytometric bead array immunoassay (Human Inflammatory Cytokine Kit, BD Biosciences, Franklin Lakes, NJ) with a detection limit of 20.0 pg/mL; levels below this limit were considered to be 0. Case versus control comparisons were made using the Mann-Whitney *U*-test. The local ethics committees approved the study.

Delirium was diagnosed in 15 patients. Nine had delirium preoperatively, and seven additional patients developed delirium postoperatively; one patient who had preoperative delirium recovered after surgery. Mean ages and Charlson Comorbidity Index scores did not differ between cases and controls. A history of dementia (n = 7) was associated with a higher incidence of delirium ($P = .008$).

Only levels of IL-8 and IL-6 were detected in CSF above the assay detection limit: IL-8 in 33 of 36 samples, and IL-6 in three of 36 samples. (IL-6 levels were not further analyzed.) Delirium cases (n = 15) had higher CSF IL-8 (median 69.8 pg/mL, interquartile range (IQR) 47.9–125.6) than controls (n = 21; median 39.6 pg/mL, IQR 28.0–64.5; Mann-Whitney $U = 68$, $P = .003$) (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 (median 42.4 pg/mL, IQR 28.9–438.4) than controls (median 24.3 pg/mL, IQR 0–217.2; $U = 6$;

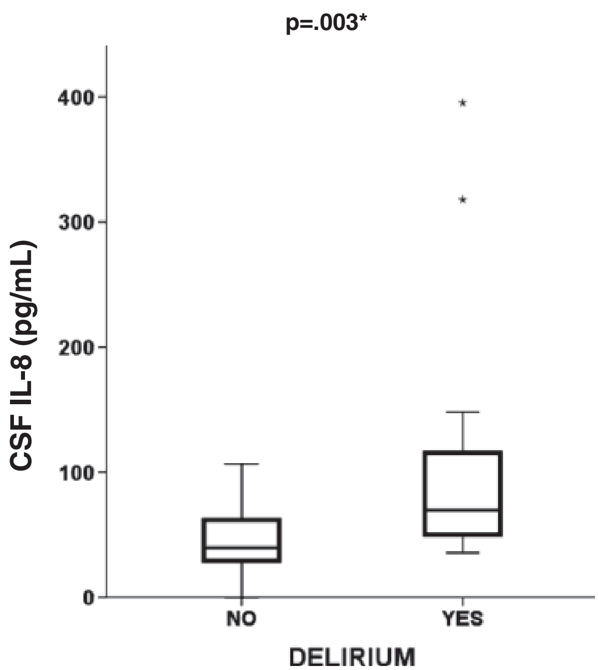

Figure 1. Cerebrospinal fluid (CSF) interleukin (IL)-8 levels (pg/mL) in patients with (n = 15) and without (n = 21) perioperative delirium.*Statistical test: Mann-Whitney $U = 68$, $P = .003$.

$P = .01$). Exclusion of the seven patients with dementia did not change the pattern of results, with 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 ($P > .10$).

The present study suggests the possibility that delirium is associated with greater CNS production of IL-8. The findings are also consistent with some other studies that have found higher serum IL-6 levels in people with 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 proinflammatory actions.[8] Although peripheral CXCL1 can cross the blood–brain barrier, synthesis by brain endothelium in response to systemic inflammation is significant.[9] Another recent study of people with hip fracture, in which mental status was not assessed and 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), supported CNS production of IL-8.[10] Taken together, these findings suggest that CNS production of IL-8 induced by peripheral inflammatory stimuli may be linked with delirium. 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.

Alasdair M.J. MacLullich, BSc, MRCP(UK), PhD
Edinburgh Delirium Research Group
Centre for Cognitive Ageing and Cognitive Epidemiology
University of Edinburgh
Edinburgh
Scotland, UK

Benjamin T. Edelshain, BSc
Edinburgh Delirium Research Group
University of Edinburgh
Edinburgh
Scotland, UK

Roanna J. Hall, BSc, MRCP (UK)
Edinburgh Delirium Research Group
University of Edinburgh
Edinburgh
Scotland, UK
Centre for Cognitive Ageing and Cognitive Epidemiology
University of Edinburgh
Edinburgh
Scotland, UK

Annick de Vries, BSc, PhD
Biomedical Sciences
KU Leuven
Leuven, Belgium

Sarah E.M. Howie, BSc, PhD
Centre for Inflammation Research
University of Edinburgh
Edinburgh
Scotland, UK

Andrew Pearson, BSc, MB ChB
Scott D. Middleton, MB ChB
Fiona Gillies, MB ChB
Edinburgh Delirium Research Group
University of Edinburgh
Edinburgh
Scotland, UK

Ian R. Armstrong, MB ChB, FRCA
Department of Anaesthetics
Royal Infirmary of Edinburgh
Edinburgh
Scotland, UK

Tim O. White, MB ChB, FRCS, MD
Department of Trauma and Orthopaedics
Royal Infirmary of Edinburgh
Edinburgh
Scotland, UK

Colm Cunningham, BSc, PhD
School of Biochemistry and Immunology
Trinity College Dublin
Dublin, Ireland

Sophia E. de Rooij, MD, PhD
Department of Internal Medicine
Academic Medical Centre
University of Amsterdam
Amsterdam, the Netherlands

Barbara C. van Munster, MD, PhD
Department of Internal Medicine
Academic Medical Centre
University of Amsterdam
Amsterdam, the Netherlands
Geriatrics Department
Gelre Hospitals
Apeldoorn, the Netherlands

ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

This study was funded by a Medical Research Council (MRC) Clinician Scientist Fellowship to AM and a Research into Ageing Research Training Fellowship to RH. The work was undertaken at the University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross-council Lifelong Health and Wellbeing Initiative. Funding from the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, and MRC is gratefully acknowledged.

Author Contributions: AM, AdV, SdR, and BvM conceived the study, led its design and coordination, and contributed to writing the manuscript. BE, AP, SM, FG, BvM, and AM performed the delirium assessments and assays and contributed to writing the manuscript. TW, IA, SH, and CC

participated in the design and coordination of the study and contributed to writing the manuscript.

Sponsor's Role: None.

REFERENCES

1. MacLullich AMJ, Ferguson KJ, Miller T et al. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. J Psychosom Res 2008;65:229–238.
2. Murray C, Sanderson DJ, Barkus C et al. Systemic inflammation induces acute working memory deficits in the primed brain: Relevance for delirium. Neurobiol Aging 2010 May 12 [Epub ahead of print].
3. van Munster BC, Korevaar JC, Zwinderman AH et al. Time-course of cytokines during delirium in elderly patients with hip fractures. J Am Geriatr Soc 2008;56:1704–1709.
4. de Rooij SE, van Munster BC, Korevaar JC et al. Cytokines and acute phase response in delirium. J Psychosom Res 2007;62:521–525.
5. Beloosesky Y, Hendel D, Weiss A et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. J Gerontol A Biol Sci Med Sci 2007;62A:420–426.
6. Adamis D, Lunn M, Martin FC et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. Age Ageing 2009;38:326–332.
7. Pearson A, de Vries A, Middleton SD et al. Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls. BMC Res Notes 2010;3:33.
8. Semple BD, Kossmann T, Morganti-Kossmann MC. Role of chemokines in CNS health and pathology: A focus on the CCL2/CCR2 and CXCL8/CXCR2 networks. J Cereb Blood Flow Metabol 2010;30:459–473.
9. Thornton P, McColl BW, Greenhalgh A et al. Platelet interleukin-1 alpha drives cerebrovascular inflammation. Blood 2010;115:3632–3639.
10. Chuang D, Power SE, Dunbar PR et al. Central nervous system interleukin-8 production following neck of femur fracture. ANZ J Surg 2005;75:813–816.

EFFECT OF BEDROOM SIZE ON FALLS IN HOSPITAL: DOES ONE SIZE FIT ALL?

To the Editor: Hospital design has been moving from large, open-plan wards to multibed bays,[1] and now single-room design policies are being implemented in hospitals in a number of countries (e.g., the United Kingdom, the United States, and Australia[2–4]). The reasons for this approach are commonly attributed to infection control, reduction of medical errors, greater privacy, provision of personalized space, and noise control,[5,6] but the evidence for these reasons has been found to be lacking or conflicted.[7] Without disputing the importance of these reasons, there is an opposing view that takes into account older individuals who run a higher risk of falls,[8] and those for whom the company of a fellow patient may be beneficial.[9]

Improving patient observation is a commonly used strategy for those at risk of falls and injury. In our experience of establishing a study on flooring for fall-related injury prevention, policies to place high-risk patients in rooms with good line of sight from the nursing station appear widespread,[10] yet there is a dearth of empirical evidence on room type for patient safety, particularly with respect to falls.[7,8] Serendipitously, the double relocation of a local elderly care general rehabilitation ward provided an ideal opportunity to assess the influence of bedroom type on falls.

Fall rates on an elderly care unit, which was moved from a facility arranged in four four-bed bays and eight single rooms (Period A, 12 months, 8,760 patient bed-days; Period B, 10 months, 6,623 patient bed-days), to a second facility with a 15-bed open-plan ward and a single side room (Period C, 13 months, 6,755 patient bed-days), and then to a third facility arranged in three four-bed bays and six single rooms (Period D, 12 months, 6,387 patient bed-days) were retrospectively analyzed. Routine operational processes, policies, and staff turnover did not change during the study period. There was one major staff change with the appointment of a new consultant in Period B. Bed:nurse ratio was predominantly consistent across the study periods (Period A, unknown; Period B, 1.45; Period C, 1.46; Period D, 1.48). Before each move, the number of patients in the ward was reduced to 15.

Patient falls data were retrieved from the standard incident-report monitoring system. The mean incidence rates of falls per 1,000 patient bed-days over the four study periods (Periods A, B, C, and D) were 13.3 ± 6.1, 14.0 ± 8.0, 5.9 ± 3.8, and 15.8 ± 9.8, respectively. After square root transformation, analysis of variance indicated a significant difference in fall rates between periods ($F = 5.10$, degrees of freedom (df) = 3, $P = .005$). This effect was also apparent when the data were analyzed using the Kruskal-Wallis test ($H = 12.32$, $df = 3$, $P = .006$, adjusted for ties). Subsequent pair-wise comparisons suggest that the open plan ward (Period C) had significantly lower fall rates than the wards with four-bed bays and single rooms (Period A, $P = .002$; Period B, $P = .008$; Period D, $P = .01$). Figure 1 demonstrates the trend in fall rates over time.

This study is retrospective and based on standard audit data and as such does not incorporate data on individual patient characteristics or recurrent fallers. The built and designed environment (e.g., room and ward size) is in a dynamic system with the social environment (e.g., staffing levels and skills) and patient characteristics (e.g., case mix). Changing one component will change the dynamic of the system and alter its outcomes.

With regard to hospital room size, there are a variety of qualitative studies on patient preferences (e.g.,[9]) along with a large volume of "expert" opinion cited,[7] based on rea-

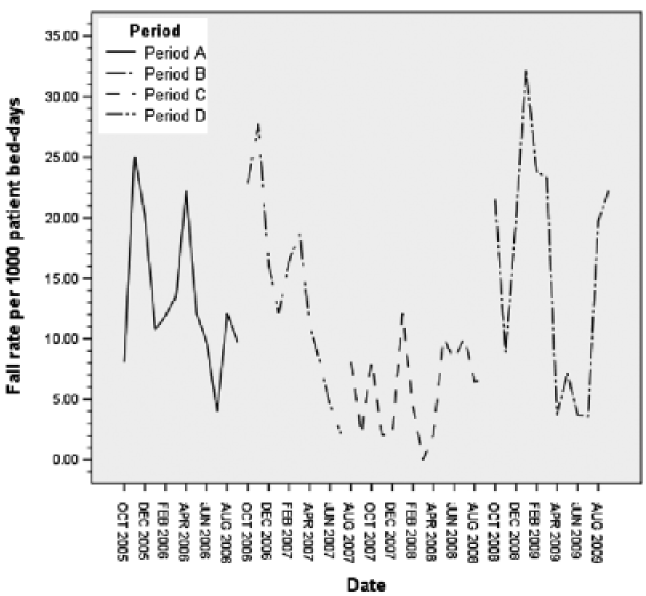

Figure 1. Trend in fall rates (per 1,000 patient bed-days). Period A, four four-bed bays and eight single rooms; Period B, same facility as Period A plus new consultant; Period C, 15-bed open-plan ward and a single side room; Period D, three four-bed bays and six single rooms.