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Depressive symptoms are associated with reduced neutrophil function in hip fracture patients ☆

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ABSTRACT

Hip fracture is a common trauma in older adults with a high incidence of depression, which relates to poorer prognosis including increased risk of infection. Ageing is accompanied by reduced immunity, termed immunesenescence, resulting in increased susceptibility to infection. We examined whether physical trauma (hip fracture) and psychological distress (depressive symptoms) had additive effects upon the aged immune system that might contribute to poor outcomes after injury. Neutrophil function was assessed in 101 hip fracture patients (81 female) 6 weeks and 6 months after injury and 43 healthy age-matched controls (28 female). Thirty eight fracture patients had depressive symptoms at 6 weeks. No difference in neutrophil phagocytosis of *Escherichia coli* was observed between controls and hip fracture patients, but superoxide production was significantly reduced in hip fracture patients with depressive symptoms compared with patients without symptoms ($p = .001$) or controls ($p = .004$) at 6 weeks. Superoxide production improved 6 months following fracture to the level seen in controls. We detected elevated serum cortisol, reduced dehydroepiandrosterone sulphate (DHEAS) and an increased cortisol:DHEAS ratio in fracture patients with depressive symptoms compared with patients without depressive symptoms or controls at 6 weeks and 6 months after injury. Serum IL6, TNFα and IL10 were higher among patients with depressive symptoms at 6 weeks. The cortisol:DHEAS ratio and IL6 levels related to depressive symptom scores but not to neutrophil function. In conclusion, depressive symptoms related to poorer neutrophil function after hip fracture, but this was not driven by changes in stress hormone or cytokine levels.

1. Introduction

Hip fracture is a devastating condition and a major health issue in old age (Abrahamsen et al., 2009). In the UK alone 370,000 older adults fall each year and 76,000 of these falls result in hip fracture (Johnell et al., 1992). Even though hip fracture is treatable, it is a severe physical stressor for older individuals accompanied by increased mortality (Roberts and Goldacre, 2003), immobilisation and physical disability (Magaziner et al., 2000) resulting in loss of independence and impaired quality of life. The factors contributing to poor outcome after hip fracture remain poorly understood.

Healthy older individuals have been reported to experience greater levels of stress, anxiousness and depression than young adults (Luz et al., 2003). Stressful life events such as bereavement, or a disabling medical event are amongst the most potent factors that can trigger depressive symptoms (Cole and Dendukuri, 2003) and are both more likely to occur in old age. It is perhaps not surprising that a high rate of depression (9–47%) has been reported in UK and US based studies of older adults with hip fracture (Holmes and House, 2000). Importantly, depression in hip fracture patients has been associated with increased risk of infections and poor survival (Nightingale et al., 2001), impaired recovery and a retarded ability to regain pre-fracture levels of physical functioning (Mossey et al., 1990).

It is well documented that ageing is accompanied by immune dysregulation (Dorshkind et al., 2009; Panda et al., 2009), termed immunesenescence, which contributes to the increased risk of infection in old age (Gavazzi and Krause, 2002). Interestingly, there is accumulating evidence suggesting that the effects of stress and age are interactive, with chronic stress exacerbating the effects of ageing in older adults (Kiecolt-Glaser and Glaser, 1999). For example, a study examining the effect of the chronic stress of care giving on vaccine responses reported that even though there was a deficit in the vaccine response of young caregivers when compared with

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young controls, this defect was magnified in older adults who were caregivers (Kiecolt-Glaser et al., 1996). Additionally, our previous study reporting a negative association between exposure to stressful life events such as bereavement and marital dissatisfaction and antibody responses to vaccination, reported a significant positive effect of marital satisfaction on the response to vaccination in older adults (Phillips et al., 2006). Our own work has also shown that innate immunity is susceptible to the effects of stress, with neutrophil superoxide generation reduced in old hip fracture patients (Butcher et al., 2003) and bereaved older adults (Khanfer et al., 2011).

The hypothalamus–pituitary–adrenal (HPA) axis acts as a pivotal regulator of the stress responses by mobilising energy reserves and modulating immune responses (Tsigos and Chrousos, 2002). Glucocorticoids (GCs), namely cortisol in humans, are key effectors of the HPA axis and are potent immune suppressors. Dehydroepiandrosterone sulphate (DHEAS), a major steroid produced by the adrenal gland, has been reported to have anti-depressive, anti-glucocorticoid and immune-enhancing properties, including increased neutrophil superoxide generation (Hazeldine et al., 2010; Radford et al., 2010). Some previous studies have suggested that healthy ageing is accompanied by hyperactivation of the HPA axis, especially in situations of chronic stress resulting in prolonged exposure to cortisol (Aguilera, 2011). However, studies examining the effects of ageing on diurnal cortisol secretion have yielded conflicting results, with either a flattening of the diurnal pattern of secretion with increasing age (Deuschle et al., 1997; Luz et al., 2003; Van Cauter et al., 1996; Yen and Laughlin, 1998), no association (Edwards et al., 2001; Wolf et al., 2002), or decreased overall levels (Orentreich et al., 1992; Straub et al., 2000) with age. In contrast, the serum level of DHEAS reaches peak concentrations during the third decade of life, after which a steady decline occurs with age (1–2% per year); such that by the age of 80, DHEAS levels have reached 10–20% of their peak level (Vermeulen, 1995). Therefore, the current literature suggests that although serum cortisol may not increase markedly with ageing, cortisol levels are higher in relation to other hormones such as DHEAS and ageing is accompanied by an elevated cortisol:DHEAS ratio which may be a key factor contributing towards age associated immune dysregulation (Buford and Willoughby, 2008) and which might be heightened by chronic stress. In a previous study, our group reported a raised cortisol:DHEAS ratio in old hip fracture patients compared to comparable young trauma patients and this enhanced glucocorticoid response was also accompanied by reduced neutrophil superoxide generation and increased incidence of infection (Butcher et al., 2005). This study did not consider other factors that might influence immunity after hip fracture. Further, both ageing ((Franceschi et al., 2007; Krabbe et al., 2004)), and depression (Dowlati et al., 2010; Leonard, 2010; Zunszain et al., 2012) are accompanied by a switch towards a pro-inflammatory state, which can be seen in the levels of different pro- and anti-inflammatory cytokines. These cytokines have profound effects on immune cells and might also influence neutrophil function (Hellberg et al., 2011).

The present study sought to test the hypothesis that psychological distress, specifically depressive symptoms, would act additively with the physical stress of hip fracture to amplify the effect of ageing upon immunity (immunesenescence), with specific reference to neutrophil function. It also examined the role of the cortisol:DHEAS ratio and pro- and anti-inflammatory cytokines as potential mediators of any additive effects observed.

2. Methods

2.1. Participants

One hundred and one older hip fracture patients (two participants were excluded after consenting as it became apparent that they did not in fact meet the inclusion criteria) were recruited from five hospitals in Birmingham, UK between 2010 and 2012. Thirty-seven (26%) were male. Inclusion criteria were that participants had to be aged 60 years and over with a hip fracture sustained 4–6 weeks previously but with no chronic immune-related disorders e.g., cancer, diabetes, or taking any regular medications that might modify immunity, e.g., immunosuppressants, statins. Additionally patients must not have had any diagnosis of depression by a physician prior to age 50 years or be taking or have previously taken anti-depressant medication, in order to pick up patients with depressive symptoms emerging post-hip fracture rather than those with a prior history of and thus propensity to depression. Participants started on anti-depressant treatment, therapy, or any change that would mean they no longer met the inclusion criteria between week 6 and month 6 testing sessions were excluded. Forty-three healthy older adults, 17 male, (40%), were also recruited from the community as controls via invitation letters to the Birmingham 1000 Elders cohort of healthy older adults involved in current research at the University of Birmingham. These controls also had to meet the inclusion criteria above but not have a current hip fracture. The study was approved by South Birmingham Local Research Ethics Committee and all participants provided written informed consent (study ref: 09/H1203/80).

2.2. Study design and procedure

The study was a prospective case-control design with three groups of older adults: hip fracture patients with or without depressive symptoms and healthy older adults. Consent was gained whilst patients were still in hospital. All patients provided a blood sample and completed questionnaires and structured interviews 4–6 weeks and 6 months after hip fracture. Control participants attended the University, at the same time as we were sampling a hip fracture patient, for one-off blood sampling and completed a depression and anxiety symptoms scale and basic demographic information (see below) following the blood sample. Blood samples were taken between 09.00 and 11.00 to minimise any effect of diurnal variations in steroid levels. None of the participants had an acute infection at the time of blood sampling. Interviews were performed either in the hospital or in the patient's home for hip fracture patients and at the university for control participants. Assays for neutrophil phagocytosis and superoxide production were performed on the same day as blood sampling. Serum was frozen for later hormone and cytokine analysis. Cytokines were only assessed at the six week time point.

2.3. Interview and questionnaires

Standard socio-demographic and health behaviour information were taken and all comorbidities and medications, prescription and over-the-counter, were recorded by the interviewer. The psychological status of the participant was assessed by means of standardised psychometric questionnaires. Depression was evaluated by a Geriatric Depression Scale (GDS) (Yesavage et al., 1982). Depression was defined as a GDS score greater than or equal to 6 (Sheikh and Yesavage, 1986). The Hospital Anxiety and Depression Scale (HADS) was also used to measure depression and anxiety (Zigmond and Snaith, 1983). The scale contains 14 items, scored from 0 (not present) to 3 (considerable), with seven assessing aspects of depression and seven assessing anxiety. Healthy control participants completed the HADS depression sub-scale in order to check that they did not have significant depressive symptoms. A cut-off of $\geqslant 8$ has previously been used to indicate possible depression (Bjelland et al., 2002).