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Albumin and depression in elderly stroke survivors: An observational cohort study

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ABSTRACT

Background/objectives: Post-stroke depression affects approximately one third of stroke survivors. In non-stroke affected populations, depressive symptomatology is associated with hypoalbuminemia. This is also common among stroke survivors and associated with poor outcome and increased mortality. The role of stroke-associated hypoalbuminemia in post-stroke depression is not clear. We aimed to explore the relationship between serum albumin and post-stroke depression, as measured 20 months post-stroke.

Subjects/methods: Observational cohort study of elderly Swedish patients drawn from the 'Gothenburg 70+ Stroke Study' ($n=149$) and assessed at 20 months after stroke onset. Serum albumin was drawn from venous blood and analysed with gas chromatography/mass spectrometry. Depressive symptomatology was assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) and functional impairment was assessed using the Barthel Index.

Results: Analysis of covariance analysis showed that serum albumin levels were associated with depressive symptoms at 20 months after stroke. Multivariate analysis of covariance showed that disability scores at 3 days were associated with depressive symptoms at 20 months after stroke and after accounting for the age covariate. Stroke survivors were not clinically deficient in serum albumin.

Conclusions: Low serum albumin appears to be associated with depressive symptoms in elderly individuals long term post-stroke.

1. Introduction

Ischaemic stroke is a leading cause of death and disability worldwide, annually affecting 15 million people (WHO, 2004). Stroke has high associated societal costs and greatly impacts the quality of life of individuals and their families (WHO, 2004). Thus post-stroke management strategies aimed at achieving best possible recovery are necessary. Depressive disorder is extraordinarily prevalent among stroke survivors, affecting approximately one third of individuals (Linden et al., 2007). In addition to lowering quality of life and overall well-being, depression following stroke is associated with poor recovery and functional capacity (Masskulpan et al., 2008).

In non-stroke-affected populations, depression is characterised by a chronic, low-grade inflammatory response, oxidative and nitrosative stress and neuroprogression (Berk et al., 2011; Leonard and Maes, 2012; Moylan et al., 2014a; Moylan et al., 2013b).

Individuals with depression have higher circulating levels of pro-inflammatory cytokines including Interferon-γ (INF-γ) (Maes, 2008) Interleukin-1*beta* (IL-1β) (Thomas et al., 2005) Tumour necrosis factor-*αlpha* (TNF-α) (Tuglu et al., 2003) and Interleukin-6 (IL- 6) (Alesci et al., 2005). Inflammatory Interferon-α (INF-α), which is routinely used for the treatment of cancer and viral infections, induces depressive symptoms in patients (Capuron and Miller, 2004) and the associated depressive symptoms terminate with cessation of INF-α therapy (Capuron and Dantzer, 2003).

Inflammation is associated with increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Both ROS and RNS are produced during normal physiologic processes and are involved in the regulation of cellular function, however can cause cellular dysfunction due to damage to lipids, proteins, deoxyribonucleic acid (DNA) and mitochondria when produced in excess (Moylan et al., 2013a, 2014b). The production of antioxidants and antioxidant enzymes, which normally counterbalance the damaging effects of ROS and RNS, is lowered in depressive disorder, resulting in an increased risk of mitochondrial

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dysfunction (Moylan et al., 2013b, 2014a).

The neuroprogression model of depression highlights that as depressive episodes are associated with cellular damage that contributes to neuronal apoptosis, decreased neurogenesis and plasticity (Moylan et al., 2013a, 2014b), that depression results in progressive functional decline over time, and increased likelihood of recurrence and treatment resistance (Moylan et al., 2013b). Indeed, the importance and contributory role of lipoprotein oxidation and subsequent cellular dysfunction in disease progression has previously been highlighted in the study of neurodegenerative Alzheimer's disease (Arlt et al., 2001; Greilberger et al., 2008; Sultana et al., 2006)

Acute phase proteins (APPs) are synthesized by the liver and are referred to as positive APPs if they increase in response to inflammation and as negative APPs if they decrease in response to inflammation (Maes et al., 1993). Clinical depression is associated with higher levels of positive APPs such as haptoglobin, C-reactive protein and complement factors (Maes et al., 1993) and a decreased concentration of negative APPs such as serum albumin, in peripheral blood samples (Ecanow et al., 1973; Huang, 2002; Huang and Lee, 2007; Hung et al., 2011; Van Hunsel et al., 1996). Serum albumin is the most abundant protein in human blood plasma and is essential in multiple functions, including the maintenance of osmotic pressure and pH and the transportation of fatty acids and hormones (Brown, 1977). Low albumin, or hypoalbuminemia, is seen in patients with treatment-resistant depression in Western countries (Van Hunsel et al., 1996) and serum albumin levels negatively correlate to the severity of depressive symptoms in patients with major depressive disorder (Huang et al., 2005), particularly with psychomotor retardation and anorexia (Maes et al., 1995). This is likely due, at least in part to increased oxidative stress, as Albumin represents a major and predominant antioxidant and much of total serum antioxidant properties can be attributed to albumin (Bourdon and Blache, 2001).

Hypoalbuminemia results from many factors including age, malnourishment and chronic disease and thus is especially common in elderly individuals who are hospitalized (Goldwasser and Feldman, 1997; Jensen et al., 2010a). Previous research indicates that in clinical depression, lowered albumin levels are probably not related to malnourishment or nutritional state (Maes et al., 1991) but rather are a consequence of the immune/inflammatory response (Maes et al., 1997b, 1997c). Inflammation, which is associated with elevated resting energy expenditure and decreased expression of circulating proteins, decreases albumin levels (Bouziana and Tziomalos, 2011; Jensen et al., 2010b). Accordingly, hypoalbuminemia is common among stroke survivors (Alcazar Lazaro et al., 2013; Dziedzic et al., 2007) and is associated with poor outcome and increased mortality (Abubakar et al., 2013; Chai et al., 2008; Gao et al., 2011; Kuzuya et al., 2007).

To our knowledge, the relationship between serum albumin and depressive symptoms in stroke surviving individuals has not been sufficiently explored, especially in the longer term after stroke, when the acute inflammation-related hypoalbuminemia is likely to have resolved.

Given both that hypoalbuminemia is associated with depressive symptoms in non-stroke-affected populations, and that post-stroke depressive disorder influences outcome, we aimed to assess if albumin levels are associated with depressive symptomatology and clinical outcome, as assessed at 20 months after stroke onset.

2. Material and methods

2.1. Participants

Eligible participants were patients admitted to Sahlgrenska University Hospital Gothenburg, Sweden (between February 1, 1993, and May 17, 1994) who were 70+ years and presenting with an acute cerebrovascular neurological deficit, diagnosed by routine investigations by the physician on call and an acute computer tomography (CT) scan. Individuals were excluded from study participation if they had coma, extracerebral or subarachnoid haemorrhage, previous cerebral lesion requiring ongoing care, cerebral tumour, or a requirement for specialized neurological care, showed symptoms for more than 7 days prior to admission, or were residing in a nursing home at the time of admission. Patents were not excluded if co-morbidities were present, such as diabetes, myocardial infarction, Parkinson's disease or, multiple sclerosis. Only severely cognitively damaged patients and patients that couldn't be randomized to stroke unit or medical wards because of requirement of a special kind of facility were excluded. All participating individuals received a hospital bed in the stroke unit or an ordinary medical ward.

2.2. Study protocol

Participating individuals ($n=149$) were contacted by mail and subsequently by telephone. Hospital appointments were arranged except for cases when the participant was unable to attend ($n=15$, 10%), in which case, appointments were offered to take place in participants' homes. Written and verbal information was provided to all individuals or their nearest relatives when relevant, and informed consent was obtained. Ethics approval was granted by The Ethics Committee for Medical Research, at the University of Gothenburg.

2.3. Biomarkers collection

Serum albumin was collected 20 months after stoke from peripheral venous blood samples during the hospital appointment. Other biomarkers were also collected at this time, including the acute phase reactant C-reactive protein and the amino acid homocysteine and have been reported elsewhere (Noonan et al., 2013; Pascoe et al., 2012). Samples were collected into 5 mL gel tubes, inverted >5 times, left to coagulate, centrifuged (10 min) and assessed by photometry (Rodkey, 1965). All collection and analysis was conducted in an accredited university hospital pathology laboratory. The normal range of human serum albumin in adults was defined as 35–50 g/L. Individuals with albumin less than 35 g/L were considered to be clinically deficient.

2.4. Diagnostic criteria

A neurologist/psychiatrist blinded to the hospital's medical record conducted the assessments of depressive symptomatology 20 months after stroke, using the Montgomery–Åsberg Depression Rating Scale (MADRS) (Muller et al., 2003) and a semi-structured interview. Overall depressive scores were compiled from adjusted MADRS scores. MADRS scores were adjusted when necessary by the neurologist/psychiatrist conducting the depression assessments and occurred in circumstances where the patient's depressive symptomatology was too severe to engage during the entire assessment period or to answer all questions. If patients' symptoms were too severe to address a component of the MADRS, they received a full score for that component/question. MADRS scores are compiled based on information obtained from ten related criteria, including apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. A low score indicates little depressive symptomatology while a high score indicates more depressive symptomatology. A score below 6 indicates an absence of depression, 7–19 indicates