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Plasma insulin growth factor—1 and incident delirium in older people

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SUMMARY

Background A variety of demographic and clinical variables are acknowledged as risk factors for delirium; a syndrome thought to be mediated by abnormalities in a wide range of neurotransmitters. However, little research has been conducted in this field and the role of neuro-immunological factors as a mechanism of medication has received very little attention.
Aims To determine if low base line (on admission) IGF-1 levels (a protective cytokine released by brain cells in response to insult) is a risk factor for incident delirium in patients aged 75 and over admitted to an acute medical ward.
Method Base line demographic and clinical variables and serum IGF-1 levels were measured in a consecutive series of 100 non-delirious subjects on inpatient admission. Subjects were assessed daily regarding the development of delirium during the inpatient episode.
Results Twelve patients developed incident delirium. IGF-1 (OR: 0.822, CI: 0.69, 0.97, $p = 0.027$), pre-admission cognitive deterioration (assessed by IQCODE) (OR; 3.26, CI: 1.18, 9.04, $p = 0.023$) and depression (GDS four item: cut-off score ≥ 3) (OR; 8.99, CI 1.59,50.76, $p = 0.013$) were identified as risk factors for developing subsequent delirium.
Conclusions Despite the small size of this study our findings suggest that low, pre-morbid IGF-1 is a risk factor for subsequent delirium in this population, emphasizing the potential protective role of this anabolic cytokine and the need for replication of these findings. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — Delirium; elderly; cytokines; IGF-1; risk factors; medical inpatients

INTRODUCTION

Risk factors for delirium include advanced age (Levkoff *et al*., 1992), prior cognitive impairment and severe physical illness (O'Keefe and Lavan 1997), alcohol dependency and depression (Pompei *et al*., 1994) and a variety of drugs. Hypotheses about the patho-physiology of delirium are largely based on animal research with the strongest evidence relating to decreased cholinergic activity (Flacker and Lipsitz, 1999). However, there is increasing understanding of the importance of cytokines, which aid the immune response but can also contribute to neuronal death and cause systemic disturbances (Kronfrol and Remick, 2000). In humans, Interleukin-6 levels in the CSF are excessive early after stroke and predict the size of the brain lesion in stroke (Tarkowski *et al*., 1995). Patients given treatment with high doses of Interleukin-2 have a high incidence of delirium of 30–50% (Rosenberg *et al*., 1989). Eikelenboom and colleagues (2002) have elegantly reviewed this subject, reviewing the hypothesis of Bonhoeffer (1912) who suggested that the reason that a number of aetiological causes might produce the uniform mental syndrome of delirium might be due to a common secondary factor, an 'autotoxin', which could be produced directly in the brain. The reviewers observe that his concept of an 'autotoxin' is similar to a cytokine such as Interlukin-1 which is an endogenous pyrogen released from cells following a number of inflammatory insults. They conclude that cytokines, in particular Interleukin-1, are important in the communication between the immune system and the brain and they may be involved in the pathogenesis of delirium (Stefano *et al*., 1994). A number of animal studies have demonstrated that cytokines can cause a

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reduction in the activity of acetylcholine observed to be reduced in delirium (Willard *et al*., 1999).

However, the primary deficit in delirium might be in the lack of a neuroprotective cytokine such as IGF-1, which inhibits the cytotoxic cytokines. For example, neural injuries such as stroke result in changes in brain IGF-1 and administration of IGF-1 immediately after such insults reduces secondary neuronal loss (Gluckman *et al*., 1998). In vitro, low concentrations of the cytotoxic cytokine TNF-α reduces the capacity of IGF-1 to promote survival in cerebellar neurons (Venters *et al*., 1999). IGF-1 has a protective role in attenuating cognitive deficit in brain-injured rats (Saatman *et al*., 1997) and enhancing neuronal development (Brooker *et al*., 2000). These observations suggest that the neuroprotective characteristics of IGF-1 may be seminal in preventing the onset of delirium in vulnerable subjects, as reviewed recently (Broadhurst and Wilson, 2001). Thus, we propose that delirium is the clinical manifestation of disruption of neuroendocrine homeostasis and the aim of this study is to test this model by examining the relationship between pre-morbid IGF-1 levels and subsequent development of the syndrome.

METHOD

This was a prospective study of 100 consecutively admitted patients aged 75 and over, suffering from significant physical illness. Patients were recruited from two acute medical wards at a general university hospital between January 2000 and March 2001. Admissions to the ward were through A&E, or via GP referral. This study had local ethical approval.

Inclusion/exclusion criteria

Significant medical illness was determined by APACHE 11 score of > 8 (Knaus *et al*., 1985). Exclusion criteria included diagnoses of delirium on admission using the Confusion Assessment Method Instrument (CAM) (Inouye *et al*., 1990) and subsequently defined by DSM-III delirium criteria (Cole *et al*., 2003), conducted by a trained psychiatrist. Patients were also excluded if they suffered from insulin dependant diabetes (Attia *et al*., 1999) or if they had hearing or visual deficits preventing them from completing psychometric assessment, if they were discharged or transferred within 48 hours (preventing blood sampling and follow-up), if they were receiving blood transfusions or so profoundly ill that they could not communicate or provide consent.

Assessments

On admission demographic and clinical details were recorded. This included the listing and classification of medication on admission and during inpatient care. Drugs were classified as having a high, medium or low propensity to cause delirium (Rolfson, 2002). The APACHE 11 was used to assess physical illness. Each patient was interviewed using the Confusion Assessment Method (CAM) Instrument which is used to screen for delirium, it is sensitive at 94%–100% while values for specificity are lower at 90%–95% (Inouye *et al*., 1990) thus it rarely misses cases but is more prone to identifying false positives and needs to be combined with a diagnostic instrument such as DSM-III. (Cole *et al*., 2003). Base line cognitive impairment was assessed using the Mini Mental State Examination (MMSE) (Folstein *et al*., 1975). The short version of the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE) (Jorm, 1994) was used to establish cognitive change over time prior to admission. Interviews were conducted with next of kin or carer. Patients were screened for depression using the short version of the Geriatric Depression Scale (GDS) (Van Marwijk *et al*., 1995) and for alcohol dependency using the CAGE questionnaire (Magruder-Habib *et al*., 1993).

A trained research assistant using the CAM instrument, supplemented by corroborative clinical information recruited from primary nursing staff, carried out daily assessments. Symptoms of incident delirium triggered further assessment by the research psychiatrist using the DSM-III criteria (APA, 1980). Preprandial, morning plasma levels of IGF-1 were measured on admission using a Nicholas Advantage automated immunoassay analyser (Nichols Institute, San Jan Capistrano, CA, USA) employing a 2-site chemiluminescence assay, standardised against WHO 1st International Reference Preparation 87/518.

Outcomes

An episode of delirium is defined by DSM-III criteria undertaken by a trained psychiatrist, having established symptoms through screening with the CAM.

Analysis

Base line variables were examined in terms of correlations between items. A univariate analysis was conducted, examining the relationship between demographic, clinical and plasma IGF-1 variables and incident of delirium during in-patient stay. Variables with

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significant correlations were subsequently entered into a multivariate analysis. IGF-1 was treated as a continuous variable.

RESULTS

Four hundred and twenty-eight consecutive patients were assessed on admission. Of these, 13 patients were excluded as they were under the age of 75 and 44 refused consent. Twenty-two did not have severe enough physical illness (APACHE score < 9) and 23 were either in coma or so ill that they could not give informed consent. A further 31 had profound communication problems, 13 required blood transfusion and six patients had diabetes mellitus. Of the remainder, 87 patients were either discharged or transferred to other hospital within the same Trust (usually to rehabilitation wards) within 48 hours. Eighty-nine patients had delirium on admission. The remaining 100 patients were admitted into the study. No significant differences between the study sample and the excluded sample were found in terms of age or gender.

The sample consisted of 69 females and 31 males with a mean age of 84.5 (SD 4.2). The mean score on the MMSE was 25.92 (SD 3.83) on admission and 13 had a score of ≥ 3 on the four-item GDS, indicating syndromal case depression (mean score of sample: 0.83,SD 1.22). The mean APACHE 11 score for the sample was 10.68 (SD: 2.76). Only two subjects had a score of two or more on the CAGE questionnaire. The mean number of drugs associated with a high risk of delirium per subject was 0.74 (range: 0–3) and 1.66 (range 0–5) for drugs associated with medium risk.

On 13 occasions the screening instrument of the Confusion Assessment Method was thought to be positive for a case of delirium by the research assistant but when these patients were assessed using the DSM-III criteria by the psychiatrist only 12/13 were found to be true cases of delirium. Thus, 12 subjects developed delirium during the inpatient stay. The total number of drugs, taken by each patient, identified as high or moderate risk (of causing delirium) was entered into the analysis as a continuous variable. Univariate analysis of base line variables was conducted (the CAGE scores were excluded as only two subjects had a rating of two or more). Age, gender, GDS score, total number of drugs identified as moderate and high risk of promoting delirium and APACHE 11 score did not correlate with incident delirium. The MMSE [Odds Ratio (OR) 0.837, *p*-value 0.009 Confidence Intervals (CI) 0.731, 0.957], 'depression' as defined by a score of three or more on the GDS (OR 7.142, *p*-value 0.005 CI 1.836, 27.786), IQCODE (OR; 2.812, *p*-value 0.020 CI 1.177, 6.720) and IGF-1 plasma levels (OR:0. 840, *p*-value 0.018, CI 0.727, 0.970) were found to significantly correlate with incident delirium. (Table 1).

These variables were subsequently entered into a multivariate logistic regression. This demonstrated a significant correlation between incident of delirium and the presence of depression (OR; 8.99, CI 1.59,50.76, $p = 0.013$), IQCODE (OR; 3.26, CI: 1.18, 9.04, $p = 0.023$), IGF-1 (OR: 0.822, CI: 0.69, 0.97, $p = 0.027$). The MMSE score was not significantly correlated and was dropped (Table 2).

DISCUSSION

The sample of 100 suitable subjects generated a delirium incident rate of 12%. This rate is slightly less than reported in contemporary studies in which an incidence rate, during admission of between 14% (Francis *et al*., 1990) and 30% (Levkoff *et al*., 1992) have been recorded. The low incident rates may be explained by the relatively high rates of exclusion, including the exclusion of patients too ill to provide informed consent, those receiving blood

Table 1. Univariate analysis

Base line	Odds Ratio	Std Err	*Z*	$p > z$	95% Confidence Intervals	
IGF −1	0.8406537	0.0613226	−2.38	0.017	0.7286603	0.9698602
Depressed	7.142857	4.950557	2.84	0.005	1.836212	27.78568
GDS Score	1.525332	0.3294934	1.95	0.51	0.9988327	2.329357
APACHI	0.9286329	0.109591	−0.79	0.427	0.7173387	1.15094
Age	1	0.0736244	0.00	1.00	0.8656271	1.155232
Gender	0.6	0.3707486	−0.83	0.408	0.1767235	2.014285
MMSE	0.8366527	0.057341	−2.60	0.009	0.73148721	0.9569364
IQCODE	2.811789	1.249066	2.33	0.20	1.177221	6.715949
No drugs	1.126109	0.1151664	1.16	0.246	0.921571	1.376044

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Table 2. Multiple logistic regression

Delirium	Odds Ratio	Std. Err	z	$p > z$	[95% Confidence Intervals]	
Depression	8.901429	7.859418	2.48	0.013	1.577251	50.23642
IQCODE	3.238831	1.684694	2.26	0.024	1.168508	8.977284
IGF-1	8230575	0.0725354	−2.21	0.027	0.6924916	0.978241

Number of observations: 89, LR chi2 (3) = 16.90, Prob > chi2 = 0.0007, Log likelihood = −22.82625.

transfusions, those with profound communication disorders and patients with diabetes mellitus. We also had to exclude a significant minority due to high levels of hospital discharge and transfer within 48 hours of admission, prohibiting appropriate research assessment and follow-up. Despite the differences in incident rates, most studies have found similar clinical and demographic risk factors, including pre-morbid cognitive impairment and depression. Nevertheless, as this study was not designed to identify incident or prevalence rates of delirium, we limit our aims to determining the relationship between biological and clinical variables and subsequent delirium. We also recommend caution in generalising our findings to more severely ill patients.

Evidence of premorbid, chronic cognitive impairment (as represented by the IQCODE) was found to be of significant predictive value. This is commensurate with the findings of other studies (Francis *et al*., 1990). The MMSE examination score was dropped from the multivariate analysis, highlighting the relative importance of the history of cognitive decline (as represented by the IQCODE) in establishing a diagnosis of dementia. This is not surprising in that third party observations regarding progressive or fluctuating cognitive impairment are acknowledged as sensitive and may provide a better representation of sustained cognitive impairment in older people suffering from acute physical ill health in the process of admission to an acute medical inpatient environment. Depression was also of significant predictive value. Its association with delirium has been noted by other studies (Pompei, 1994). We were unable to find a relationship between CAGE score and subsequent delirium within this sample. This may be explained by the possibility that subjects likely to suffer from alcohol dependency may have been excluded as a consequence of being delirious on admission or because of serious concomitant medical illness.

There is only a weak evidence base concerning neurotransmitters as mediators of delirium. A variety of abnormalities have been reported. Decreased cholinergic activity (Flacker and Lipsitz, 1999), and increased anticholinergic medication (Rothwell, 1991) are associated with a high risk. Hypercortisolism has been linked to the cholinergic hypothesis (O'Keefe and Devlin, 1994). Excessive dopaminergic activity has led to the use of haloperidol as a possible agent of symptomatic control (Flacker and Lipsitz, 1999).

Our study differs from this approach in that we are testing the hypothesis that the brain has an innate protection against chemical and physical insult through the production of anabolic cytokines. IGF-1 is a protective, anabolic cytokine acting at end organs. It is seminal to the GRH/somatostatin-growth hormone-IGF-1 axis and its release is controlled by feedback mechanisms. Its anabolic role has been demonstrated in animal studies, increasing the production of neurones (Asberg *et al*., 2000) and enhancing cognitive functions of rats (Saatman *et al*., 1997). A recent prospective study of comatosed, head injured patients demonstrated an IGF-1 response (De Marinis *et al*., 1999) and improved cognitive functioning has been reported in response to treatment of growth hormone deficient adults (Deijen *et al*., 1998). Not surprisingly, raised levels of cytokines occur in common causes of delirium such as cancer, infection, heart failure and infection (Neibauer *et al*., 1999).

What evidence there is suggests that a variety of demographic and clinical variables diminish this protective response, engendering a vulnerability to the development of delirium. Our finding that long-term premorbid cognitive impairment, as described by the IQCODE as a risk factor for delirium, is consistent with this. The neuro-protective role of IGF-1 has been established in a wide range of diseases including those in which reduced cholinergic activity is evident (Dore *et al*., 2000) which is further countered by increased levels of cytotoxic cytokines in these conditions. The ageing process is recognised as a potential risk factor in delirium and is associated with reducing IGF-1 levels. In healthy older men, low serum levels of IGF-1 correlate with impaired cognitive performance

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and both serum levels and cognitive performance improve on treatment with growth hormone.

There are relatively few studies examining the relationship between IGF-1 and depression in this age group. Studies that have been conducted in adults of working age suggest that IGF-1 is likely to be increased in depressive disorder (Deuschle *et al*., 1997). This suggests even though the growth hormone axis is implicated in the aetiology of depression, reduced IGF-1 neuroprotection is unlikely to play an important part and other mechanisms are required to explain the link between depression and subsequent delirium.

CONCLUSION

We propose that delirium is the clinical manifestation of disruption of neuro-endocrine homeostasis. Our finding of an association between low baseline IGF-1, premorbid cognitive impairment and incident delirium supports this model. Older, ill subjects are particularly vulnerable as low IGF-1 levels are directly associated with increasing age, longstanding cognitive impairment and chronic physical disease. The evidence points towards a vital lower threshold of IGF-1 level in the aging brain, which is further compromised by chronic ill heath and cognitive impairment. Below this level, the brain is vulnerable to cytotoxic effects of cytokines generated by advent of acute physical illness, presenting with consequent delirium.

IGF-1 may have a direct role in the management and prevention of delirium (Saatman *et al*., 1997). Other evidence suggests that physical exercise may be an indirect method of promoting endogenous IGF-1 prophylaxis. Inouye (2000) demonstrated the protective role of exercise (in conjunction with a number of other interventions) in the prevention of delirium in medically ill in-patients. Regular intensive exercise in older male subjects is associated with higher growth hormone and more specifically, an increase in IGF-1. Despite the relatively small size of this study, our findings suggest that IGF-1 may play an important role in protecting older people from subsequent delirium. If our findings are replicated, low base line IGF-1 may be a suitable marker of future delirium and present an opportunity for prophylaxis and possible intervention.

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