Abstract

Introduction: Late life depression is known to be associated with specific clinical features, such as cognitive impairments, to have a poor outcome and to be a risk factor for future dementia. Vascular factors have been implicated in aetiology, but neuroinflammation has not been well studied despite being a highly plausible mechanism and potentially tractable target. In our previous work we have shown an increase in inflammatory cytokines in the blood in older depressed subjects, In the current study we aimed to show whether we could demonstrate an increase in central (brain) inflammation in vivo using PET imaging.

Methods: Within the Cambridge Neuroimaging of Inflammation in MemoRy and Other Disorders (NIMROD) study we have recruited 5 older depressed subjects who had met DSM-IV criteria for major depression and 13 controls. Subjects had full clinical and cognitive assessment and venipuncture for CRP measurement. Brain imaging was performed with PET for 75 minutes following bolus iv injection of \$^{[11C]}$PK11195 (500MBq) and multi-modal 3T MR imaging was also undertaken. Using regional reference tissue modelling of the dynamic PET data corrected for CSF contamination, non-displaceable binding potential (BPND) was estimated using region of interest analysis.

Results: Depressed subjects (Dep) and controls (Con) did not differ in age, sex ratio, education or global cognition (MMSE score) but had significantly higher blood CRP levels than controls (mean (SD): Dep 6.4 (5.1); Con 1.0 (1.2); p<0.05). Though largely recovered from their depression at time of imaging, depressed subjects had significantly raised \$^{[11C]}$PK11195 BPND compared to controls in several regions (for example, anterior cingulate mean (SD): Dep 0.118 (0.061); Con 0.025 (0.067); p = 0.025).

Conclusions: We found evidence of both central and peripheral inflammation in older subjects with depression, with changes in areas including the anterior cingulate, known to play a key role in the regulation of mood. Neuroinflammation may be an important mechanism in late life depression and merits further investigation as a potential target for novel therapeutics in a condition which responds poorly to conventional antidepressant therapy.

Speaker 2: Gwenn Smith, USA

Title: Molecular Imaging of Serotonin Degeneration and Alzheimer Neuropathology in Late Life Depression and Mild Cognitive Impairment

Gwenn S. Smith, PhD, Frederick S. Barrett, PhD, Alena Savonenko, MD, PhD, Yun Zhou PhD, Dean F. Wong MD, PhD, Clifford I. Workman, PhD

Abstract

The neurobiological substrates underlying the transition from normal aging and mild cognitive impairment (MCI) to Alzheimer’s disease (AD) are poorly understood, as are the mechanisms underlying the role of late-life depression (LLD) that is associated with increased risk of cognitive decline. AD pathology is associated with cognitive impairment and functional decline in both MCI and LLD. Substantial advances in neuroimaging instrumentation and radiotracer chemistry have enhanced the ability to study in vivo an increasing number of neurotransmitters, neuromodulators, and, importantly, neuropathological processes. This is an unprecedented opportunity to understand the neurobiology of early stage AD by testing mechanistic hypotheses derived from human post-mortem data and transgenic amyloid mouse models in the living human brain in the preclinical stages of AD. An understanding of the neurobiology of the early course of AD and of clinical progression is critically needed to identify individuals at risk, as well as to identify therapeutic targets for prevention and treatment. Several lines of evidence strongly support the investigation of serotonin degeneration associated with beta-amyloid deposition (Aβ). Transgenic amyloid mouse models show selective vulnerability of cortical monoamine projections, serotonin to a greater extent, in contrast to modest cortical and hippocampal neuronal loss. The pattern of MA degeneration in the mice is remarkably similar to MA pathology in Alzheimer’s disease (AD) and parallels the course of cognitive deficits in the mice. Serotonergic deficits are a consistent finding in AD and in recent neuroimaging studies in LLD and MCI. Multi-modality molecular imaging methods were employed to test these observations from the mouse models in patients with LLD, MCI and normal controls. MCI, LLD and demographically matched normal controls underwent clinical and cognitive evaluations, magnetic resonance imaging and high resolution positron emission tomography (HRRT) with well-established radiotracers for the serotonin transporter (SERT, \$^{[11C]}$-DASB), Aβ (\$^{[11C]}$-PiB) and regional cerebral blood flow ([rCBF; \$^{[15O]}$-water), respectively). SERT binding was correlated with cognitive measures (verbal and visuospatial memory).

Reduced 5-HTT was observed in MCI and LLD compared to controls in cortical and limbic areas affected by AD pathology, as well as sensory and motor areas, striatum and thalamus that are typically spared. The reduction in 5-HTT was greater and more extensive than grey matter atrophy or reduced rCBF in both groups compared to controls. Lower cortical SERT was associated with worse performance in tests of verbal and visuospatial memory, to a greater extent in MCI than controls.

The decrease of SERT in MCI and LLD observed in the present study, suggests that the serotonin system may represent a target for prevention and treatment, particularly the post-synaptic receptors (5-HT4 agonists, 5-HT5 antagonists) that may not be as severely affected as SERT. Studies are in progress to determine whether serotonin degeneration may be involved in the MCI to dementia transition and whether serotonin degeneration is related to other aspects of AD neuropathology.

Speaker 3: Hideshi Yamashita, Japan

Title: Vascular neuropathology in geriatric psychiatry - depression, cognitive disturbance, and dementia

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Abstract

A growing body of evidence supports an association between cerebrovascular disease and geriatric depression. The term “vascular depression” has been used to describe a subtype occurring later in life and characterized by brain changes that may be related to depression onset.

Over previous decades, several generations of hypotheses have linked depression to the etiology or pathophysiology of dementia.

The likely biological mechanisms linking depression to dementia include vascular disease, alterations in glucocorticoid steroid levels and hippocampal atrophy, increased deposition of amyloid-β plaques, inflammatory changes, and deficits of nerve growth factors.
The relationship between depression and both dementia and cerebrovascular pathology has, for good reason, received much attention from researchers and clinicians alike.

This presentation focused on relevant findings of neuroanatomical pathways and associated monoaminergic abnormality in vascular depression, apathy, cognitive dysfunction, and pathway linking depression, apathy to cognitive dysfunction, and dementia.

We examined the relationships between post-stroke depression (PSD), functional recovery, cognitive functioning, and lesion location, after separating PSD into two core symptom dimensions: Affective (depressive) and apathetic (loss of interest). These two core symptom dimensions appear to have different underlying neuroanatomical mechanisms, and appear to exert different effects on cognitive functioning and functional recovery. Among the patients with higher depressive scores, the lesion overlap centered on the brainstem, left basal ganglia, and left frontal cortex. Among the patients with higher apathy scores, the lesion overlap centered on the brainstem and bilateral striatum. And apathy was a better predictor of poor functional recovery after a stroke than depression although apathy and depression both affect negatively on cognitive functioning. It is therefore important that studies of PSD consider the two symptoms dimensions separately.

Next, we investigated relationship between abnormality of neuroanatomical pathways, and monoaminergic abnormality in PSD patients. Findings indicated that depression and apathy scores did not correlate with monoamine, and or metabolite values. However, the decrease of NA&DA and the increase of NA&DA turnover were related to lesions in the brainstem, whereas the increase in NA&DA and the decrease in NA&DA turnover were related to cortical and/or striatum lesions. The data on 5-HT turnover showed an opposite tendency to NA&DA turnover. Results of our studies on vascular depression and apathy may indicate catecholamine (NA&DA) and serotonin, both of which are anatomically and functionally interconnected and could respectively influence apathetic, and affective symptoms of depression after stroke.

Speaker 4: Hochang Lee, USA
Testing Vascular Depression hypothesis: Neuropsychiatric Outcomes after Heart Surgery (NOAHS) Study

Abstract
Depression after coronary artery bypass graft (CABG) surgery is common (up to 40%) and increases risk of cardiac morbidity and mortality in the first year by more than two fold. However, current scarcity of data on etiopathogenesis of post-CABG depression hampers development of prevention or treatment strategies of post-CABG depression. “Vascular Depression” hypothesis posits that cerebrovascular disease predisposes, precipitates, or perpetuates late-onset depression and implicates etiopathogenesis and treatment strategies that are different from idiopathic, early-onset depression. Conspicuous similarities in demographics, longitudinal course, and presence of vascular risk factors exist between post-CABG depression and vascular depression. The NIMH-sponsored Neuropsychiatric Outcomes after Heart Surgery (NOAHS) study utilizes Transcranial Doppler ultrasound (TCD) to detect and quantify the location and severity of Intracranial Atherosclerosis (ICA), as well as to assess for other putative pre-CABG risk factors (e.g. pre-CABG depression, neuroticism, low social and support) for post-CABG depression in CABG surgery patients at the time of cardiac catheterization. The NOAHS study tests the Vascular Depression Hypothesis by follow the subjects over the subsequent 12 months to assess for incidence, symptomatology and course of post-CABG depression. Confirming these predictions will support the hypothesis that post-CABG depression is a form of Vascular Depression, thus laying the foundation for risk stratification with a mobile, bedside tool and development of etiologically-based prevention strategies to reduce morbidity and mortality associated with post-CABG depression.

CP05: Schizophrenia

Speaker: Gerhard Grunder, Germany
Speaker: Sung Wan Kim, Republic of Korea

Abstract
Early intervention services for the first episode schizophrenia are shown to be effective for symptomatic and functional outcomes. Early intervention has two objectives: The first is to prevent the onset of schizophrenia in individuals at ultra-high risk. The second is to provide effective treatment to people in the early stages of schizophrenia, with the goal of reducing the ultimate severity of the illness. The functioning of patients with schizophrenia spectrum disorders often declines within 3–5 years of the onset of this illness and plateaus thereafter. Therefore, the first 3–5 years of this disorder have been described as a critical period during which the future course and prognosis of the patient is determined. The guidelines of the National Institute for Health and Care Excellence (NICE) in the UK recommend that a full range of pharmacological, psychological, social, occupational, and educational interventions be provided for people with psychosis. A key element of the psychological interventions for people with first-episode psychosis is cognitive–behavioural treatment (CBT). There is less evidence for early intervention for people with early psychosis in Asian countries compared with Western countries. This presentation provides an overview of early intervention services for psychosis. Leading Korean early intervention programs in Gwangju Bukgu Mental Health Center are demonstrated. Group cognitive-behavioral therapy (CBT), intensive cognitive behavioral case management with smartphone application, and nutritional support have been conducted for early psychosis. Those early intervention services were effective for the improvement of psychotic symptoms and functional impairment in patients with early psychosis. Integration of psychosocial treatment based on community mental health center and pharmacotherapy based on hospital is important for comprehensive treatment for psychosis.

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