EDITORIAL

Late-onset depressive disorders: a preventable variant of cerebrovascular disease?[1]

The severe depressive disorders of late life are associated with high rates of medical morbidity and mortality, cognitive impairment, suicide, disability, complex treatment regimens, institutionalization and high costs to the community (Murphy, 1983; Murphy *et al.* 1988; Bruce & Leaf, 1989; NIH Consensus Development Panel, 1992; Alexopoulos *et al.* 1993 *a*, *b*; Brodaty *et al.* 1993; Bruce *et al.* 1994; Forsell *et al.* 1994; Hickie *et al.* 1995; Blazer, 1996). Those disorders that are accompanied by cognitive impairment and/or concurrent medical morbidity have a particularly poor outcome (Bruce & Leaf, 1989; Alexopoulos *et al.* 1993 *b*; Hickie *et al.* 1995, 1997 *a*). Although psychosocial models of late-life depression place considerable importance on age-related psychological and social risk factors, those who survive into later life may actually be characterized by psychological resilience (Henderson, 1994; Blazer, 1997).

Current aetiological research in late-life depression, therefore, places particular emphasis on the potential role of biological risk factors. The potential importance of vascular risk factors is receiving renewed attention and may provide opportunities for specific prevention and intervention strategies in high-risk populations. This emphasis on possible vascular risk factors, and the wider importance of vascular pathologies in late-life neuropsychiatric disorders, mirrors the emphasis of much earlier clinico-pathological studies (Binswanger, 1894; Alzheimer, 1895). The specific focus on the importance of small progressive changes within the subcortical white matter, as distinct from more discrete cortical infarcts (Olszewski, 1962), is now supported by the emerging neuroimaging literature and theoretical constructs in late-life depression (Krishnan, 1991, 1993; Hickie *et al.* 1996, 1997 *b*; Krishnan *et al.* 1997).

IDENTIFYING RISK FACTORS FOR LATE-LIFE DEPRESSION

Clinical and neuroimaging studies in late-life depression now highlight the relevance of current age and age of onset (Coffey *et al.* 1990; Krishnan, 1991, 1993; Alexopoulos *et al.* 1993 *a*; Krishnan *et al.* 1995; Hickie *et al.* 1995, 1996; Brodaty, 1996). The validity of the proposed distinction between early-onset (typically less than 50 years) and late-onset primary depressive disorders is being tested against clinical features, neurobiological correlates, genetic and biochemical risk factors, treatment response and longitudinal course. Phenomenologically, a subgroup of older patients with severe depression is characterized by severe psychomotor change, psychotic features and cognitive impairment (Brodaty *et al.* 1991; Brodaty, 1996). However, few clinical differences exist between those older patients who have either the early-onset or late-onset subtype (Alexopoulos *et al.* 1988; Alexopoulos, 1990; Krishnan *et al.* 1995; Brodaty, 1996), indicating that if age-associated risk factors are operative they cannot be identified simply by specific clinical features. As the familial risk to depression declines with age of onset (Mendlewicz, 1976; Mendlewicz & Baron, 1981), late-onset disorders are also more likely to be a consequence of pathologies whose incidence increases with age, such as neurodegenerative and vascular diseases. Therefore, non-clinical strategies such as neuroimaging, biochemical studies or genetic screening may be necessary to detect these age-associated pathogenic processes.

DEPRESSION AND DEMENTIA SYNDROMES

Older patients with severe depression often present with pronounced cognitive impairment, the so-called 'dementia of depression' syndrome (Folstein & McHugh, 1978; Alexopoulos *et al.* 1993*b*). Although traditionally classed as 'pseudodementias' (Kiloh, 1981), longitudinal studies demonstrate that a significant subproportion do develop irreversible cognitive impairment, chronic depression and residual disability (Alexopoulos *et al.* 1993*b*; Hickie *et al.* 1997*a*). Major depression does not appear to be a central feature of dementia of the Alzheimer type (Brodaty & Luscombe, 1996) and when depressive symptoms do occur during the course of a primary dementia syndrome, it is likely that the dementia has a vascular aetiology (Ballard *et al.* 1996). Longitudinal studies emphasize the medical morbidity and mortality experienced by patients with depressive disorders, particularly in older patients, where cardiovascular and cerebrovascular diseases are important (Hickie *et al.* 1993; Bruce *et al.* 1994).

Overt cerebrovascular disease, including stroke, is particularly associated with increased rates of affective disorder (Robinson *et al.* 1984, 1988). Longer-term studies also suggest that depressed patients may be at increased risk of dementia, and that such dementias are likely to be of the vascular type (Luscombe *et al.* 1995; Hickie *et al.* 1997*a*). Importantly, recent epidemiological evidence confirms that hypertension is a risk factor to dementia (Skoog *et al.* 1996), probably due to disruption of cortical–subcortical paths. Patients with cognitive impairment are also at increased risk of later overt stroke, suggesting that cerebrovascular disease plays a larger role in the aetiology of late-onset dementias than previously suspected (Ferrucci *et al.* 1996).

MAGNETIC RESONANCE IMAGING (MRI) IN LATE-LIFE DEPRESSION

Magnetic resonance imaging (MRI) studies demonstrate that older patients with severe depression have a range of abnormalities including loss of cerebral volume with preferential reduction in frontal cortex, increased lateral ventricular size, reduction in the volume of the caudate and putamen nuclei, and an increased prevalence of extensive subcortical white matter hyperintensities (SWMHs) (Coffey *et al.* 1988, 1989, 1990, 1993; Krishnan *et al.* 1988, 1992, 1997; Figiel *et al.* 1991; Hussain *et al.* 1991; Brown *et al.* 1992; Krishnan, 1993; Fujikawa *et al.* 1994; Hickie *et al.* 1995; Greenwald *et al.* 1996; O'Brien *et al.* 1996; Kumar *et al.* 1997; Simpson *et al.* 1997). These studies suggest that relevant risk factors for extensive SWMHs are: a diagnosis of depression; older age; older age of onset; risk factors to cerebrovascular disease (notably hypertension and diabetes); treatment-resistance; and, concurrent medical morbidity. Consistent with the notion of late-onset disorders resulting from age-related pathologies, patients with extensive SWMHs do not have increased family histories of affective disorder (Hickie *et al.* 1995; Krishnan *et al.* 1997). Similar subcortical changes on MRI have been reported in other neurodegenerative disorders, notably Alzheimer's disease (AD), but the prevalence of extensive lesions within the deep white matter is clearly increased relative to age-matched controls only in patients with depression and/or those with concurrent vascular risk factors (Fazekas *et al.* 1987; Brown *et al.* 1992; Kumar *et al.* 1992; Erkinjuntti *et al.* 1994; O'Brien *et al.* 1996).

While the pathological significance of SWMHs on MRI was initially debated, histopathological studies suggest that small lesions represent vascular ectasia and expansion of perivascular spaces (i.e. non-pathological age-related changes), while larger punctate and more diffuse lesions involve demyelination of axons, axonal degeneration, proliferation of oligodendroglial cells, the presence of occasional macrophages (consistent with tissue damage) and, less frequently, discrete micro-infarction (Awad *et al.* 1986; Braffman *et al.* 1988; Marshall *et al.* 1988; Fazekas *et al.* 1993; Scheltens *et al.* 1995). The deep white matter is particularly susceptible to such degenerative changes as it is perfused by small perforating arterioles that are prone to the adverse long-term effects of hypertension and diabetes. The neuropathological changes suggest a spectrum of vascular impairment ranging from chronic hypoperfusion to episodes of 'neurologically-silent' micro-infarction and, eventually, widespread subcortical leucoencephalopathy ('Binswanger's disease').

Periventricular changes, however, appear to be a consequence of breakdown in the ventricular ependyma, with leakage of cerebrospinal fluid into the white matter.

The clinical significance of extensive SWMHs in late-life depression has become increasingly apparent. Extensive SWMHs are associated with psychomotor slowing and a pattern of 'subcortical' rather than 'cortical' neuropsychological impairment in normal older subjects (Ylikoski *et al*. 1993), patients with vascular risk factors (Junque *et al*. 1990) and patients with depression (Hickie *et al*. 1995; Hickie, 1996; Lesser *et al*. 1996; Salloway *et al*. 1996). SWMHs predict delirium in response to antidepressant therapies (Figiel *et al*. 1991), a poorer clinical response to standard treatment regimens, including ECT (Hickie *et al*. 1995), and a poorer longitudinal course with high rates of residual disability and institutionalization (Hickie *et al*. 1997*a*). Importantly, in a significant minority of patients, extensive SWMHs predict the development of irreversible cognitive impairment consistent with a vascular aetiology (Hickie *et al*. 1997*a*).

IDENTIFYING GENETICALLY-DETERMINED RISK FACTORS

The identification of the $\epsilon4$ isoform of apolipoprotein E (Apo E) as a risk factor for AD (Saunders *et al*. 1993*a, b*) has intensified the search for other genetic and biochemical risk factors which may predispose to late-onset neuropsychiatric disorders. While genetic factors appear to play a large role in determining the risk to AD, environmental factors and specific gene–environment interactions (e.g. smoking, dietary behaviours) appear to be much more relevant to vascular dementia (Bergem *et al*. 1997; Plassman & Breitner, 1997). Hence, identification of relevant genetic and environmental risk factors may provide the basis for highly-targeted preventative strategies.

Apo E $\epsilon4$ also has an atherogenic effect due to elevation of circulating levels of low-density lipoproteins (Davignon *et al*. 1988), and possibly via an effect on the response of the vessel wall to injury (Vogel *et al*. 1994; Wang *et al*. 1995). Increased rates of the Apo E $\epsilon4$ isoform have been detected in some studies of patients with vascular dementia (Shimano *et al*. 1989; Pedro-Botet *et al*. 1992; Noguchi *et al*. 1993; Frisoni *et al*. 1994), but not others (Betard *et al*. 1994; Kawamata *et al*. 1994; Sakoda *et al*. 1994). Most importantly, the Apo $\epsilon4$ isoform has also been detected with increased frequency in a small group of patients with late-life depression (Krishnan *et al*. 1994). Given its role in atherogenesis, and its involvement in central nervous system response to injury (Ignatius *et al*. 1987; Goedert *et al*. 1994), it is likely that Apo E $\epsilon4$ is not simply a risk factor to late-onset AD, but rather a risk factor to a wider range of pathologies which cause primary (e.g. AD) or secondary (e.g. via vascular effects) damage to neural tissue.

The evidence with regard to the vascular risks associated with Apo E $\epsilon2$ isoform is less clear. Apo E $\epsilon2$ has been consistently associated with raised triglyceride levels (Davignon *et al*. 1988), and has been associated with vascular dementia (Betard *et al*. 1994). More recently, it has been suggested that Apo E $\epsilon2$ may be a protective factor against the severity of vascular disease (Wang *et al*. 1995). It has been suggested that Apo E $\epsilon2$ is specifically associated with depressive symptomatology in late-onset AD (Holmes *et al*. 1996).

Elevations in levels of serum homocysteine have been consistently demonstrated in patients with coronary and cerebrovascular disease, while discrete hyperhomocysteinaemia has been associated with increased risk for both myocardial infarction and stroke (Wilcken *et al*. 1983; Ueland *et al*. 1992; Boers, 1994). Although a variety of conditions may result in raised homocysteine, the link with vascular disease appears to remain constant. Genetically-determined differences in the enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR) result in elevated levels of homocysteine and these have been associated with early-onset vascular disorders. Potentially, polymorphisms in the MTHFR gene may serve as markers for those at risk of vascular disease (Wilcken *et al*. 1996).

Folate and vitamins B_{12} and B_6 play a key role in homocysteine metabolism and dietary deficiency of folic acid has been associated with hyperhomocysteinaemia and atherogenesis (Selhub *et al*. 1995). It is possible that low or marginal levels of vitamins B_{12} and B_6 and/or serum folate may interact with minor, common enzymatic differences to increase the risk of vascular disease (Wilcken

et al. 1996). As many older persons have inadequate dietary consumption of folate and raised homocysteine, they may be at particular risk of vascular disease (Selhub *et al.* 1993). While the use of folate and vitamin B supplements as a preventive strategy for vascular disease awaits larger-scale replication, the possibility that such simple interventions might ameliorate the progression of cerebrovascular disease is an attractive proposition.

REDEFINING LATE-LIFE DEPRESSIONS

Advances in general medicine create opportunities for strategic research in neuropsychiatry. In the future, depressive subtypes may be defined by combinations of neurobiological features and risk factors rather than clinical features. For example, Krishnan *et al.* (1997) have recently proposed the term 'vascular depression' to identify depressed patients with concurrent deep white matter or subcortical grey matter hyperintensities on MRI. The validity of this notion is supported not only by clinical validators such as older age, later age of onset and a reduced familial rate of mental illness (Krishnan *et al.* 1997), but also by functional imaging studies which demonstrate reduced cerebral perfusion in patients with extensive white matter changes (Lesser *et al.* 1994). Krishnan *et al.* (1994) had earlier proposed another depressive subtype characterized by late-onset, cognitive impairment and presence of the Apo E ϵ4 allele. The validity of this proposed subgroup can be tested longitudinally by studying rates of progression to dementia.

As a narrower clinico-pathological entity, we have described a more restrictive depressive subtype (Hickie *et al.* 1995, 1996, 1997*a*). We emphasize the presence of observable psychomotor change, subcortical neuropsychological signs, late-onset, reduced familial rates of depression, treatment-resistance, vascular risk factors and subcortical MRI changes. Longitudinal studies support the validity of this subtype by demonstrating increased adverse effects from physical treatments, impaired response to antidepressant therapy and progression to chronic depression and dementia of the vascular type (Figiel *et al.* 1991; Hickie *et al.* 1995, 1997*a*).

Such longitudinal cohort studies, which combine relevant clinical, neurobiological, imaging and genetic factors, have the capacity to advance rapidly our understanding of the pathophysiology of these disorders. Concurrently, broader epidemiological studies are now required to determine whether hypertension, or any of the genetic risk factors to AD or vascular disease, are population-based risk factors to late-onset depression. As has been demonstrated with non-steroidal anti-inflammatory agents in AD (Breitner *et al.* 1994), such focused epidemiological studies also have the capacity to detect potential protective factors. Following such studies, it should be possible to create more exact criteria sets and/or diagnostic instruments, based on combinations of key clinical and laboratory features, which identify more specific pathophysiological entities.

PREVENTION OF LATE-ONSET DEPRESSION

If some severe late-onset depressions are actually sequelae of impaired subcortical perfusion then there is considerable scope for both primary and secondary prevention. The public health emphasis on modification of risk factors to cerebrovascular disease (Hachinski, 1992) may lead eventually to lower incidence rates of late-onset depression. Furthermore, the rapidly expanding knowledge of specific genetic risk factors to vascular disease and/or neurodegenerative processes may help to focus primary prevention strategies on high-risk populations. Adequate evaluation of vascular risk factors should also be incorporated into the clinical assessment of patients with late-onset depression, as progression of an underlying vascular pathophysiology appears to increase the rate of disability, institutionalization and progression to vascular-type dementia (Hickie *et al.* 1997*a*). Standard clinical features (smoking history, blood pressure, diabetes) may need to be augmented by pursuit of relevant dietary history and laboratory (e.g. serum folate, homocysteine, presence of antiphospholipid antibodies) features. Modification of known risk factors to cerebrovascular disease in patients with late-onset depression, in addition to simple interventions such as folate and

vitamin B supplementation, may help to reduce the rate of disease progression, improve longitudinal course and reduce the rate of progressive cognitive impairment.

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