International Psychogeriatrics (2004), 16:1, 3–8 © 2004 International Psychogeriatric Association
DOI: 10.1017/S1041610204000002X Printed in the United Kingdom

GUEST EDITORIAL

Criteria are needed for research in vascular depression

Introduction

There has been longstanding interest in the relationship of depression to vascular disease and this has received renewed interest since the publication of the "vascular depression" hypothesis by Alexopoulos and colleagues (Alexopoulos *et al.*, 1997). They proposed that cerebrovascular disease (CVD) predisposed, precipitated or perpetuated late-life depression by its impact on frontal-subcortical circuits (FSC). However, whilst several lines of research strongly support this proposal, we still have no useful working criteria for vascular depression, assuming such a nosological entity exists.

Depression and vascular disease

High rates of depression occur in association with vascular diseases, with typical rates of major depression being 15–20% after myocardial infarction (Frasure-Smith *et al.*, 1993), 20–30% following stroke (Pohjasvaara *et al.*, 1998) and in association with vascular dementia (Ballard *et al.*, 2000a). Strong evidence that there is a biological link between depression and these diseases has come from cohort studies which have rated depression at baseline in healthy subjects and followed them up to examine whether depression predicts the development of vascular disease. There are now at least 12 such community cohort studies examining whether depression is a risk factor for coronary artery disease (CAD) and myocardial infarction (MI) and, after controlling for known risk factors, nine have reported that depression is an independent risk factor which increases CAD by two- to fourfold (Thomas *et al.*, 2003a). Similarly, there are six such studies for stroke disease and five have found depression to increase subsequent stroke (Thomas *et al.*, 2003a). Such findings suggest there are close patho-physiological links between depression and vascular disease, which may involve the frequently reported abnormalities in the hypothalamic pituitary adrenal (HPA) axis (O'Brien *et al.*, 1993) and the immune-inflammatory response in both depression (Kronfol, 2002) and vascular disease (Ridker *et al.*, 2002).

Not only is depression frequent after stroke, but the anatomical location of the stroke may be important, as Robinson and colleagues have reported a number of studies associating depression with left hemispheric and frontal stroke (Morris *et al.*, 1996; Robinson *et al.*,1984; Robinson *et al.*, 1985). The implication is that CVD impacting on the FSC is especially likely to lead to depressive illness. Other

studies have tended not to support these findings, e.g. Gonzalez-Torrecillas *et al.*, (1995) and so in a systematic review (Carson *et al.*, 2000) concluded there was no evidence of an association of left-hemisphere stroke and depression or of an association of depression with left anterior lesions or with frontal lesions in general. However, a recent large study from Finland may have re-opened the debate. (Vataja *et al.*, 2001) assessed depression at 3 to 4 months after ischemic stroke in 275 subjects (mean age 71) who all received a MRI scan. They found depression (both major and minor) in 40% of these patients, and they showed a significant increase in both the number and the volume of infarcts affecting the FSC, especially on the left side. This thorough study included a large number of subjects and, because MRI rather than CT imaging was used, it was able to accurately examine the location and size of infarcts. It provides important new evidence for an association of frontal infarcts, especially those impinging on the FSC, with poststroke depression.

Earlier MRI studies in primary depression have repeatedly demonstrated that signal hyperintensities in the white and subcortical grey matter are associated with depressive illness. O'Brien *et al.* reviewed 19 studies up to 1996, mainly of elderly subjects, with the main findings being of a strong association between increased numbers and severity of hyperintensities in the deep white matter (DWMH), especially in the frontal lobes, and depression. Subsequent studies have supported these findings and strengthened the evidence for an association of depression with hyperintensities located in the basal ganglia and frontal lobes, e.g. (Greenwald *et al.*, 1996). All of these studies examined clinical samples from secondary and tertiary care facilities, but two community MRI studies of elderly people have now reported an increase in hyperintensities in late-life depression. In the Cardiovascular Health Study, severity of white matter change and basal ganglia lesions were both significantly associated with depression but, after adjusting for confounders, only the link with basal ganglia lesions remained significant (Steffens *et al.*, 1999). The Rotterdam Scan Study (de Groot *et al.*, 2000) reported WMH to be strongly associated with depression, with someone with severe WMH having a three- to fivefold increase in the likelihood of having depression. These studies demonstrate that increased signal hyperintensities in depression are not confined to clinical samples of depressed people with more severe illness and therefore appear to be of wider relevance to the pathophysiology of late-life depression.

The assumption has been that these hyperintensities are due to CVD and hence their increase in depression supports the vascular depression model. We have reported neuropathological evidence that DWMH are due to cerebral ischemia. In a neuroimaging-neuropathological correlative study to examine the neuropathological basis of WMH in depression (Thomas *et al.*, 2002b), we found that all the DWMH examined in the depressed subjects showed evidence

https://doi.org/10.1017/S104161020400002X Published online by Cambridge University Press

of hypoxia-ischemia, whilst this was true of less than a third of lesions in control subjects. This highly significant difference was due largely to smaller punctate lesions (<3 mm in diameter), which were ischemic in depressed subjects, but usually not in control subjects. Larger DWMH were usually ischemic in both groups. Furthermore, ischemic DWMH showed a marked specificity for the white matter at the level of the dorsolateral prefrontal cortex (DLPFC) in the depressed group (Thomas *et al.*, 2002b). Some periventricular hyperintensities (PVH) showed evidence of cerebral ischemia, especially when they were larger, but other causes, most frequently secondary to ependymal loss, were common (Thomas *et al.*, 2003b). These findings indicate that not only are DWMH increased in elderly people with depression, but there is also an increase in the proportion of DWMH due to ischemia, and this implies that the burden of ischemia due to DWMH is underestimated by MRI comparisons of depressed and control subjects. The same applies to DWMH in the frontal lobe. MRI studies show DWMH are more common in the frontal lobes in depression (O'Brien *et al.*, 1996), but these findings show such frontal lesions are also more likely to be due to cerebral ischemia in elderly depressed subjects. Thus depression may be more closely linked to vascular disease than clinical risk factors show.

Studies examining the vascular depression concept

Since the vascular depression hypothesis was published, the proposal has been examined by at least two research groups taking very different, but complementary, approaches. Lyness and colleagues in Rochester assessed cerebrovascular risk factors and depression in both secondary (Lyness *et al.*, 1998) and primary care patients (Lyness *et al.*, 1999) and reported no association of depression with vascular disease. They followed up the primary care patients for a year and found that a higher baseline score for cerebrovascular risk factors was significantly and independently associated with both the one-year diagnostic group and the one-year Hamilton Depression Rating Scale (HAM-D) score (Lyness *et al.*, 2000). However, the former difference was reduced to only a trend level when initial diagnosis and Hamilton Depression Rating Scale (HAM-D) score were controlled for, but the latter remained significant. These findings lend only limited support to the view that clinically determined vascular disease is associated with depression and are consistent with earlier similar reports, e.g. Greenwald *et al.*, (1996).

In Newcastle, we have reported a series of pathological analyses of vascular depression in a group of 20 elderly subjects (mean age 74) with major depression, comparing them with 20 psychiatrically healthy control subjects. None of the subjects had clinical or neuropathological evidence consistent with a dementia.

https://doi.org/10.1017/S104161020400002X Published online by Cambridge University Press

We found atheromatous disease at post-mortem was greater in the depressed subjects, with most of the difference resulting from increases in disease affecting the cerebral vessels (Thomas *et al.*, 2001). These depressed subjects also showed an increase in both intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 (Thomas *et al.*, 2002a; Thomas *et al.*, 2000) in tissue from the DLPFC, in both the grey and underlying white matter. This increase is consistent with post-ischemic inflammation being more severe in the depressed subjects and thus with an increase in CVD. Consistent with this we have also found an increase in astrocytic activity, measured using glial fibrillary acid protein (GFAP), in the cortex of the DLPFC (Davis *et al.*, 2002). As well as supporting the vascular depression hypothesis, these findings again suggest that clinically determined measures of CVD may be insensitive for detecting the full burden of cerebrovascular pathology because, in spite of these pathological differences, there were no group differences in vascular risk factors (Thomas *et al.*, 2001).

Suggested research criteria for vascular depression

What is striking in these studies is the discrepancy between the clinical studies, which show little evidence of a relationship between vascular disease and depression, and other research which strongly supports such a relationship. The neuroimaging and neuropathological evidence provide clear evidence for ischemic and inflammatory changes in the FSC in depressive illness and the community cohort studies support this, yet ratings of vascular risk factors in depressed subjects do not show the expected increases. It is important to remember, however, the insensitivity of clinical measures in detecting CVD when considering these negative findings and, furthermore, the vascular factors examined have been those used for stroke, and might not be the most appropriate. For example, causes of hypotension were not assessed in these studies in spite of their being common and a recognized cause of cognitive decline and signal hyperintensities on MRI (Ballard *et al.*, 2000b). Thus, incorporating hypotension in future clinical criteria might be useful. Others have suggested adding MRI evidence of hyperintensities to try to more accurately delineate a vascular depression subgroup (Krishnan *et al.*, 1997; Taragano *et al.*, 2001), and this appears a reasonable way forward. However, using broad measures of hyperintensities will probably not be helpful, as Krishnan *et al.*, (1997) were not able to distinguish a clinical vascular depression group using their criteria. Given the robust evidence associating depression with frontal, especially FSC changes, it may be more important to include lesion location (in the frontal lobes and basal ganglia), combined with some measure of lesion severity to discriminate a vascular depression group. For progress in research, subjects with vascular depression might be defined as fulfilling DSM-IV criteria for major

https://doi.org/10.1017/S104161020400002X Published online by Cambridge University Press

depression, having a first episode after 60 and showing frontal or basal ganglia hyperintensities with a Scheltens score of *f*2 (that is, periventricular WMH >5 mm or multiple punctate WMH or larger lesions) (Scheltens *et al.*, 1993). At the present time, the absence of working clinical criteria limits the usefulness of the vascular depression concept for clinicians, but, if vascular depression can be supported as a distinct subgroup, using such criteria this may lead to the development of refined clinical criteria, probably including neuroimaging evidence of hyperintensities, that delineate a clinically distinct group for whom vascular treatments may be beneficial.

ALAN THOMAS
Institute for Aging and Health
Newcastle-upon-Tyne, UK
Email: A.J.Thomas@newcastle.ac.uk

References

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., and Charlson, M. (1997). "Vascular depression" hypothesis. *Archives of General Psychiatry*, 54, 915–922.

Ballard, C., Neill, D., O'Brien, J., McKeith, I. G., Ince, P., and Perry, R. (2000a). Anxiety, depression and psychosis in vascular dementia: prevalence and associations. *Journal of Affective Disorders*, 59, 97–106.

Ballard, C., O'Brien, J., Barber, B., *et al.* (2000b). Neurocardiovascular instability, hypotensive episodes, and MRI lesions in neurodegenerative dementia. *Annals of the New York Academy of Sciences*, 903, 442–445.

Carson, A. J., MacHale, S., Allen, K., *et al.* (2000). Depression after stroke and lesion location: a systematic review. *Lancet*, 356, 122–126.

Davis, S., Thomas, A., Perry, R., Oakley, A., Kalaria, R. N., and O'Brien, J. T. (2002) Glial fibrillary acidic protein in late life major depressive disorder: an immunocytochemical study. *Journal of Neurology, Neurosurgery & Psychiatry*, 73, 556–560.

de Groot, J. C., de Leeuw, F., Oudkirk, M., Hofman, A., Jolles, J., and Breteler, M. B. (2000): Cerebral white matter lesions and depressive symptoms in elderly adults. *Archives of General Psychiatry*, 57, 1071–1076.

Frasure-Smith, N., Lesperance, F., and Talajic, M. (1993). Depression following myocardial infarction. Impact on 6-month survival. *JAMA*, 270, 1819–1825.

Gonzalez-Torrecillas, J. L., Mendlewicz, J., and Lobo, A. (1995). Effects of early treatment of poststroke depression on neuropsychological rehabilitation. *International Psychogeriatrics*, 7, 547–560.

Greenwald, B. S., Kramer-Ginsberg, E., Krishnan, R. R., Ashtari, M., Aupperle, P. M., and Patel, M. (1996). MRI signal hyperintensities in geriatric depression. *American Journal of Psychiatry*, 153, 1212–1215.

Krishnan, K. R., Hays, J. C., and Blazer, D. G. (1997). MRI-defined vascular depression. *American Journal of Psychiatry*, 154, 497–501.

Kronfol, Z. (2002). Immune dysregulation in major depression: a critical review of existing evidence. *The International Journal of Neuropsychopharmacology*, 5, 333–343.

Lyness, J. M., Caine, E. D., Cox, C., King, D. A., Conwell, Y., and Olivares, T. (1998): Cerebrovascular risk factors and later-life major depression. Testing a small-vessel brain disease model. *American Journal of Geriatric Psychiatry* 6, 5–13.

https://doi.org/10.1017/S104161020400002X Published online by Cambridge University Press

Lyness, J. M., Caine, E. D., King, D. A., Conwell, Y., Cox, C., and Duberstein, P. R. (1999). Cerebrovascular risk factors and depression in older primary care patients: testing a vascular brain disease model of depression. *American Journal of Geriatric Psychiatry*, 7, 252–258.

Lyness, J. M., King, D. A., Conwell, Y., Cox, C., and Caine, E. D. (2000). Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. *American Journal of Psychiatry*, 157, 1499–501.

Morris, P. L., Robinson, R. G., Raphael, B., and Hopwood, M. J. (1996). Lesion location and poststroke depression. *Journal of Neuropsychiatry & Clinical Neurosciences*, 8, 399–403.

O'Brien, J., Ames, D., and Schweitzer, I. (1993). HPA axis function in depression and dementia: a review. *International Journal of Geriatric Psychiatry*, 8, 887–898.

O'Brien, J. T., Ames, D., and Schwietzer, I. (1996). White matter changes in depression and Alzheimer's Disease: A review of magnetic resonance imaging studies. *International Journal of Geriatric Psychiatry*, 11, 681–694.

Pohjasvaara, T., Leppavuori, A., Siira, I., Vataja, R., Kaste, M., and Erkinjuntti, T. (1998). Frequency and clinical determinants of poststroke depression. *Stroke*, 29, 2311–2317.

Ridker, P. M., Rifai, N., Rose, L., Buring, J. E., and Cook, N. R. (2002). Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events.[comment]. *New England Journal of Medicine*, 347, 1557–65.

Robinson, R. G., Kubos, K. L., Starr, L. B., Rao, K., and Price, T. R. (1984). Mood disorders in stroke patients. Importance of location of lesion. *Brain*, 107, 81–93.

Robinson, R. G., Starr, L. B., Lipsey, J. R, Rao, K., and Price, T. R. (1985). A two-year longitudinal study of poststroke mood disorders. *Journal of Nervous & Mental Diseases*, 173, 221–226.

Scheltens, P., Barkhof, F., Leys, D., *et al.* (1993). A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *Journal of the Neurological Sciences*, 114, 7–12.

Steffens, D. C., Helms, M. J., Krishnan, K. R., and Burke, G. L. (1999). Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke*, 30, 2159–166.

Taragano, E., Allegri, R., Vicario, A., Bagnatti, P., and Lyketsos, C. G. (2001). A double-blind, randomized clinical trial assessing the efficacy and safety of augmenting standard antidepressant therapy with nimodipine in the treatment of "vascular depression". *International Journal of Geriatric Psychiatry*, 16, 254–60.

Thomas, A. J., Ferrier, I. N., Kalaria, R. N., Davis, S., and O'Brien, J. T. (2002a). Cell adhesion molecule expression in the dorsolateral prefrontal cortex and anterior cingulate cortex in major depression in the elderly. *British Journal of Psychiatry*, 181, 129–134.

Thomas, A. J., Ferrier, I. N., Kalaria, R. N., Perry, R. H., Brown, A., and O'Brien, J. T. (2001). A neuropathological study of vascular factors in late-life depression. *Journal of Neurology, Neurosurgery & Psychiatry*, 70, 83–87.

Thomas, A. J., Ferrier, I. N., Kalaria, R. N., *et al.* (2000). Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. *American Journal of Psychiatry*, 157, 1682–1684.

Thomas, A. J., Kalaria, R. N., and O'Brien, J. T. (2003a). Depression and vascular disease: What is the relationship? *Journal of Affective Disorders* (in press).

Thomas, A. J., O'Brien, J. T., Barber, R., McMeekin, W., and Perry, R. (2003b). A neuropathological study of periventricular white Matter hyperintensities in major depression. *Journal of Affective Disorders* (in press).

Thomas, A. J., O'Brien, J. T., Davis, S., *et al.* (2002b). Ischemic basis for deep white matter hyperintensities in major depression: A neuropathological study. *Archives of General Psychiatry*, 59, 785–792.

Vataja, R., Pohjasvaara, T., Leppavuori, A., *et al.* (2001). Magnetic resonance imaging correlates of depression after ischemic stroke. *Archives of General Psychiatry*, 58, 925–31.