

SHORT REPORT

Depression and its relation to lesion location after stroke

Siobhan M MacHale, Suzanne J O'Rourke, Joanna M Wardlaw, Martin S Dennis

Abstract

The study of discrete organic cerebral lesions resulting in clearly definable psychiatric disorders may provide an understanding of the underlying pathophysiological basis of these disorders. However, the relation between lesion location and psychiatric illness after stroke remains unclear. Fifty five patients referred to hospital were identified who had a single lesion on CT which was consistent with their neurological presentation and who did not have evidence of a persistent affective disorder at the time of the stroke. Six months after stroke standardised psychiatric assessment disclosed that 26% of the patients met DSM-IV criteria for an anxiety or depressive disorder, with depression the most common diagnosis (20%). Pathological emotionalism was diagnosed in 18% of patients, particularly those who were depressed ($p < 0.0001$). Depression was significantly associated with larger lesions involving the right cerebral hemisphere ($p = 0.01$). The importance of depression as a consequence of stroke has been clarified by the studies in this area. However, wide confidence intervals support the possibility that significant results may be due to chance. A systematic review of these studies is now needed if a consensus is to be reached.

ments used.^{1,2} Equally unclear is the relation between lesion location and psychiatric illness. With studies reporting an association between depression and left anterior lesions,³⁻⁵ right hemispheric lesions,^{6,7} or no association with right or left cerebral pathology,⁸⁻¹¹ the debate continues.

Patients and methods

One hundred and eighty seven patients referred to a city hospital with a clinical diagnosis of stroke were consecutively identified as part of a randomised trial of a stroke family care worker.¹² Criteria for inclusion into the randomised trial were inpatient or outpatient assessment at the hospital within one month of having a stroke, residence within 25 miles, consent to follow up, and likelihood of survival. Of these, 16 (9%) patients died in the first six months and seven (4%) refused follow up. A further 19 (10%) patients were excluded because of severe cognitive deficits (15 patients with a mental test score < 5)¹³ or severe aphasia (four patients) which precluded psychiatric interview. Fourteen of these 19 patients had left hemispheric lesions on CT.

Six months after randomisation, 145 (85%) survivors had a psychiatric assessment carried out at their place of residence. The schedule for affective disorders and schizophrenia (SADS), a standardised semistructured psychiatric interview,¹⁴ was used to generate a DSM-IV psychiatric diagnosis.¹⁵ Diagnoses were grouped as either depressive disorders (comprised of major depressive disorder, depressive disorder not otherwise specified, or adjustment disorder with depressed mood) or anxiety disorders (comprised of generalised anxiety disorder, agoraphobia with or without panic disorder, simple phobia or adjustment disorder with anxious mood) for the purposes of analysis. The short emotionalism questionnaire was administered to allow diagnosis of pathological emotionalism as defined in the Oxfordshire Community Stroke Project—that is, an increase in tearfulness with episodes of crying or laughter that were sudden or unheralded and not all under normal social control.¹⁶ An observer rated measure of ability to perform 10 basic activities of daily living such as dressing and eating was used to assess physical disability (Barthel index).¹⁷ Patients were also given the

Royal Edinburgh
Hospital, Edinburgh
EH10 5HF, UK
S M MacHale

Department of Clinical
Neurosciences,
Western General
Hospital, Edinburgh
EH4 2XU, UK
S J O'Rourke
J M Wardlaw
M S Dennis

Correspondence to:
Dr S M MacHale,
Department of Psychological
Medicine, The Royal
Infirmary of Edinburgh,
Lauriston Place, Edinburgh
EH3 9YW, UK.

Received 1 May 1997 and in
revised form 26 August 1997
Accepted 28 August 1997

(*J Neurol Neurosurg Psychiatry* 1998;64:371–374)

Keywords: depression; stroke

Over the past decade there has been an upsurge of interest in research into neuropsychiatric disorders after stroke. This has paralleled the expansion of biological psychiatry, based on the assumption that knowledge of discrete organic brain lesions resulting in clearly definable psychiatric illnesses will provide an understanding of the underlying pathophysiological basis of these disorders.

Both stroke and affective illnesses are common, but how often they coexist remains unclear. Reported rates of depression after stroke have ranged from 14 to 60% depending on factors such as populations sampled, time of assessment after stroke, and diagnostic instru-

Prevalence of DSM-IV depressive disorder, major depressive episode (MDE), and emotionalism at six months with respect to lesion location

	Right hemisphere (n=25)	Left hemisphere (n=30)	Anterior (n=22)	Posterior (n=33)	Right anterior (n=11)	Other (n=44)
All depression:						
Present	10	3	7	6	7	6
Absent	15	27	15	27	4	38
Odds ratio	6.0		2.1		11	
95% CI	1.4–25.2		0.6–7.4		2.5–49.7	
Fisher's	p=0.012		NS		p=0.017	
MDE:						
Present	6	2	4	4	4	4
Absent	19	28	18	29	7	40
Odds ratio	4.4		1.6		5.7	
95% CI	0.8–24.3		0.4–7.3		1.2–28.4	
Fisher's	NS		NS		p=0.042	
Emotionalism:						
Present	5	6	7	4	5	6
Absent	20	24	15	29	29	38
Odds ratio	1.0		3.4		5.3	
95% CI	0.3–3.8		0.9–13.4		1.2–22.9	
Fisher's	NS		NS		p=0.032	

hospital anxiety and depression scale (HADS)¹⁸ to complete and return by post.

Of the 145 patients, 131 (90%) had brain CT within six weeks of their index stroke. All scans were done on an IGE 8800 CT scanner with fast upgrade, using standard 10 axial slices through the whole brain at 1 cm intervals. Scans were read blind to all clinical findings by a consultant neuroradiologist (JW) and all visible stroke lesions (infarct or haemorrhage) were classified according to site, volume, and whether cortical or subcortical (depth), recent, or old. No tumours were identified. An infarct was defined as an area of low density (relative to normal brain) which occupied a vascular territory and might be swollen, atrophied, or haemorrhagic depending on its age. A haemorrhage was defined as an area of increased density, usually rounded, with mass effect. Lesion site was identified according to the hemisphere involved and anterior or posterior position according to the topographical criteria employed by Starkstein *et al.*¹⁹ Hence, the anterior location of the lesion was defined as the mean distance of the anterior border of the infarct from the frontal pole averaged over all slices in which it was visible. This measurement was then expressed as a percentage of the greatest distance between the anterior and posterior poles of the brain (A-P distance). Lesions were described as "anterior" if their anterior border was less than 40% of the A-P distance. "Posterior" lesions were defined as those in which the anterior border was posterior to 40% of the A-P distance. Lesions were subdivided into cortical or subcortical depending on depth. Volume was estimated according to the method of Pullicino *et al.*²⁰ Each of the methods described has been employed in previous studies of psychiatric morbidity after stroke.^{3 21}

Non-parametric tests of significance were used as most of the measures were not normally distributed. Fisher's exact probability test was used in tests of dichotomous variables when small numbers were involved. The Mann-Whitney *U* test allowed comparisons between groups of continuous data. Two tailed tests of probability were chosen along with a minimum significance level of $p < 0.05$. Forward stepwise regression analysis was used to

test the strength of association between depression and potentially confounding variables.

Results

All 145 patients were white, with a mean age of 66 (range 18–93), and a slight excess of men (52%). Most were married or widowed (81%) and living in their family home (96%). Three quarters (109) of the patients had never had a previous stroke and 114 (79%) required admission to hospital. Over half the patients had no residual neurological disability six months after the stroke, with the remainder either mildly (Barthel index score 15–19) disabled (33%), or moderately to severely (Barthel score < 15) disabled (15%).

Thirty eight patients (26%) met DSM-IV criteria for an anxiety or depressive disorder. Depressive illness was the most common psychiatric diagnosis, affecting 29 patients (20%). Younger patients ($U = 1201$, $p = 0.03$) and those with greater physical disability ($U = 954$, $p = 0.001$) were significantly more likely to be depressed. Pathological emotionalism was diagnosed in 26 (18%) patients. Emotionalism was significantly associated with depression ($p < 0.0001$), with 16 (62%) of these patients also meeting criteria for a depressive illness. Complete data were available for the HADS in 105 (72%) patients, with most non-completions due to either an inability to comprehend questions or failure to return the self report questionnaire. With a cut off score of 8/9, 21 patients were diagnosed as depressed on the HADS compared with 18 with the SADS, and seven had a diagnosis of anxiety (without comorbid depression) on both HADS and SADS assessment.

Of the 131 patients who had CT, 46 had no lesion visualised. On 15 scans the lesion identified was incompatible with the neurological deficits on clinical assessment. A further 10 scans were excluded because of either multiple or cerebellar lesions. Finally, five of the remaining 60 patients had a retrospective diagnosis made of an anxiety or depressive disorder at the time of their stroke and so were also excluded. The relation between psychiatric diagnoses and lesion location was then analysed in the 55 patients who had a single lesion

on CT which was consistent with their neurological presentation and who did not have evidence of a persistent affective disorder before the stroke.

Patients with right hemispheric lesions were significantly more likely than those with left hemispheric lesions to have a depressive disorder diagnosed at six months ($p=0.01$, table). Post hoc comparison disclosed that patients with right anterior lesions were more often depressed when compared with all other groups ($p=0.02$). There was no significant difference between anterior and posterior lesions overall with respect to a diagnosis of depression. Although 24% of patients with right sided lesions had a major depressive episode compared with less than 7% involving the left side, this finding was not significant. None of the 11 patients with a left anterior lesion had a depressive illness six months after their stroke.

Depressed patients had larger cerebral lesions ($z=-2.77$, $p<0.006$) but no effect of lesion depth was found. A multiple logistic regression analysis was conducted, to examine further the relation between depression as the dependent variable and potential confounders. Independent variables were lesion side, position, depth and volume, and age, sex, and level of disability. It was possible to model depression with lesion side ($p<0.02$) and level of disability ($p<0.04$) separately in a forward regression. However, once right and left hemispheric differences were accounted for, no significant effect of disability remained.

All four patients with an anxiety disorder but no depressive illness had a posterior lesion, but the small numbers involved precluded a definite conclusion.

Patients with lesions in the right anterior region had a higher frequency of emotionalism at the time of psychiatric assessment when compared with any other region ($p=0.032$, table). There was no significant relation between side, position, volume, or depth of lesion and a diagnosis of emotionalism.

Discussion

In this study we report an association between right hemispheric lesions, particularly those involving the anterior region, and depressive illness six months after stroke. Our finding that 85% of patients who survived to six months had either no or mild neurological disability is comparable with community based reports.^{9, 22} The exclusion of a number of patients in this, as in other studies,^{8, 11, 21} because of severe cognitive or communicative deficits may contribute to an underestimate of psychiatric morbidity in those patients with left hemispheric lesions. Starkstein and Robinson have suggested that aphasia does not cause depression, but the two may coexist, depending on lesion location and, as yet, there remains no reliable method of assessing mood disorders in patients with severe comprehension deficits.²³

There are reasons contributing to the lack of consensus on a possible association between lesion location and depression after stroke. Firstly, the period of time which has elapsed after the stroke is an influential factor in the

association between location of lesion and depression. Much of the work of Robinson and colleagues involved assessing patients within the first few weeks after stroke, although they also confirmed the importance of left anterior pathology in depression six months and one year after stroke.²⁴ A study which specifically considered this question reported that left anterior lesions only predicted major depression in the acute stage after stroke, but not at three or 12 months.⁵

Secondly, studies emphasising the relevance of left anterior pathology have considered more disabled inpatient populations,³⁻⁵ with neither of two recent community based studies finding a significant association between location of lesion and depression after stroke.^{9, 11} The study of Dam *et al* of a similar group of patients as ours (inpatients or outpatients at the hospital neurological department) have reported a significantly higher degree of depression in patients with right hemispheric lesions, with the highest degree of symptoms found in those with right anterior pathology.⁶

Finally, Ross and Rush have cautioned clinicians about the flattened affect and aprosodic speech which may accompany right sided lesions, causing statements of low mood "delivered in an unconvincing, flat monotone devoid of affective qualities" to be disregarded.²⁵ They have also emphasised the critical role of denial of emotional or neurological impairment in patients who have sustained a right hemispheric injury. The Robinson group's initial work required a patient's admission to feeling sad or depressed before diagnosing a depressive illness²⁶ but later reported that depression was equally frequent among patients with or without anosognosia.²⁷

This study is supportive of Lishman's²⁸ report of an association between affective disorders and both right hemispheric and frontal lobe damage after penetrating brain injury, along with that of Flor-Henry²⁹ in his localisation of affective disorders to the non-dominant lobe. In the light of these findings, it is disconcerting to read in the internationally recognised ICD-10 classification system³⁰ the following diagnostic guidelines:

"Right hemispheric organic affective disorder (changes in the ability to express or comprehend emotion in individuals with right hemisphere disorder). Although the patient may superficially appear to be depressed, depression is not usually present: it is the expression of emotion that is restricted."

The importance of depression as a consequence of stroke has been clarified by the studies in this area. However, due to the small numbers involved in individual studies incorporating heterogeneous patient populations, the role of lesion location remains unclear. Wide confidence intervals support the possibility that significant results may be due to chance. A systematic review of these studies is now needed if a consensus is to be reached.

- 1 House A, Dennis M, Mogridge L, et al. Mood disorders in the year after first stroke. *Br J Psychiatry* 1991;158:83-92.
- 2 Robinson R, Starr L, Price T. A two year longitudinal study of mood disorders following stroke: prevalence and duration at six months follow-up. *Br J Psychiatry* 1984;144:256-62.
- 3 Eastwood M, Rifat S, Nobbs H, et al. Mood disorder following cerebrovascular accident. *Br J Psychiatry* 1989;154:195-200.
- 4 Robinson R, Kubos K, Starr L, et al. Mood disorders in stroke patients: importance of location of lesion. *Brain* 1984;107:81-93.
- 5 Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A three-year longitudinal study. *Stroke* 1993;24:976-82.
- 6 Dam H, Pedersen H, Ahlgren P. Depression among patients with stroke. *Acta Psychiatr Scand* 1989;80:118-24.
- 7 Schwartz J, Speed N, Brunberg J, et al. Depression in stroke rehabilitation. *Biol Psychiatry* 1993;33:694-9.
- 8 Sinyor D, Jacques P, Kaloupek D, et al. Poststroke depression and lesion location. An attempted replication. *Brain* 1986;109:537-46.
- 9 House A, Dennis M, Warlow C, et al. Mood disorders after stroke and their relation to lesion location. *Brain* 1990;113:1113-29.
- 10 Sharpe M, Hawton K, House A, et al. Mood disorders in long-term survivors of stroke: associations with brain lesion location and volume. *Psychol Med* 1990;20:815-28.
- 11 Burvill P, Johnson G, Chakera T, et al. The place of site of lesion in the aetiology of post-stroke depression. *Cerebrovasc Dis* 1996;6:208-15.
- 12 Dennis M, O'Rourke S, Slattery J, et al. Evaluation of a stroke family care worker—a randomised control trial. *BMJ* 1997;314:1071-6.
- 13 Hodkinson H. Evaluation of a mental test score for the assessment of mental impairment in the elderly. *Age Ageing* 1972;1:233-8.
- 14 Endicott J, Spitzer R. A diagnostic interview. The schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 1978;35:837-44.
- 15 American Psychiatric Press. *Diagnostic and statistical manual of mental disorders (DSM-IV)*, 4th ed. Washington, DC: APA, 1994.
- 16 House A, Dennis M, Molyneux A, et al. Emotionalism after stroke. *BMJ* 1989;298:991-4.
- 17 Mahoney F, Barthel D. Functional evaluation: the Barthel index. *Maryland State Medical Journal* 1965;14:61-5.
- 18 Zigmond A, Snaith R. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361-70.
- 19 Starkstein S, Robinson R, Price T. Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. *Brain* 1987;110:1045-59.
- 20 Pullicino P, Nelson R, Kendall B, et al. Small deep infarcts diagnosed on computed tomography. *Neurology* 1980;30:1090-6.
- 21 Andersen G, Vestergaard K, Ingemann-Nielsen M, et al. Risk factors for post-stroke depression. *Acta Psychiatr Scand* 1995;92:193-8.
- 22 Wade D, Legh-Smith J, Hewer R. Depressed mood after stroke. A community study of its frequency. *Br J Psychiatry* 1987;151:200-5.
- 23 Starkstein S, Robinson R. Affective disorders and cerebral vascular disease. *Br J Psychiatry* 1989; 54:170-82.
- 24 Parikh R, Lipsey J, Robinson R, et al. A two-year longitudinal study of post-stroke mood disorders: prognostic factors related to one and two year outcome. *Int J Psychiatry Med* 1988;18:45-55.
- 25 Ross E, Rush A. Diagnosis and neuroanatomical correlates of depression in brain-damaged patients. *Arch Gen Psychiatry* 1981;38:1344-54.
- 26 Starkstein S, Robinson R, Honig M, et al. Mood changes after right-hemisphere lesions. *Br J Psychiatry* 1989;155:79-85.
- 27 Starkstein S, Fedoroff J, Price T, et al. Anosognosia in patients with cerebrovascular lesions. A study of causative factors. *Stroke* 1992;23:1446-53.
- 28 Lishman W. Brain damage in relation to psychiatric disability after head injury. *Br J Psychiatry* 1968;114:373-410.
- 29 Flor-Henry P. On certain aspects of the localization of the cerebral systems regulating and determining emotion. *Biol Psychiatry* 1979;14:677-98.
- 30 World Health Organisation. *The international classification of diseases [ICD-10], 10th revision. Classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: WHO, 1992.