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ORIGINAL PAPER

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Post-stroke affective or apathetic depression and lesion location: left frontal lobe and bilateral basal ganglia

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Abstract This study was designed to examine the correlation between damage to the basal ganglia or frontal lobe and depression status (both affective and apathetic dimensions) in 243 stroke patients. We assessed the affective dimension in post-stroke depression (PSD) using the Zung Self-rating Depression Scale (SDS) and the apathetic dimension in PSD using the apathy scale (AS). We classified basal ganglia or frontal lobe damage into four groups: no damage, damage to the left side only, damage to the right side only, and damage to both sides. Affective and/or apathetic PSD was found in 126 patients (51.9%). The severity of affective depression (SDS score) was associated with left frontal lobe (but not basal ganglia) damage, and that of apathetic depression (AS score) was related to damage to the bilateral basal ganglia (but not to the frontal lobe). The anatomical correlates of PSD differ depending on the PSD dimension (affective or apathetic) and may explain interstudy differences regarding the association between lesion location and type of PSD.

Key words basal ganglia · frontal lobe · stroke · apathy · Zung Self-rating Depression Scale

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Introduction

Depression is a common neuropsychiatric consequence of stroke and has been reported to negatively affect functional and cognitive recovery (Alexopoulos et al. 1997; Biringer et al. 2005). Some studies, including those on stroke patients, have demonstrated morphological changes in major depression with respect to the hippocampus, basal ganglia and frontal lobe (Alexopoulos et al. 1997; Bielau et al. 2005; Frodl et al. 2004; Sheline et al. 1996). Therefore, the neuroanatomical model of mood regulation was developed from the observation that lesions in some cortical/subcortical regions resulted in depression (Soares and Mann 1997).

"Depressed mood" is a very sensitive symptom in the diagnosis of depression (affective PSD) using Self-rating Depression (SDS), which is a widely used self-report questionnaire used to measure depression (Kitamura et al. 2004). On the other hand, "loss of interest" is a less sensitive symptom than "depressive mood" using SDS and is thought to be a component of apathy, which is often observed after stroke and is defined as reduced motivation and lack of initiative and exploration (Starkstein et al. 1993; Yamagata et al. 2004).

In the present study, we examined the affective and apathetic dimensions of post-stroke depression (PSD) separately, and evaluated their correlation with basal ganglia or frontal lobe damage in stroke patients.

Subjects and methods

Patients

The approval of our institutional ethics committee was obtained for this prospective study. Informed consent was obtained from all patients. Patients included in this study were selected from a consecutive series of 408 patients with hemorrhagic or occlusive stroke, who were diagnosed using computed tomography (CT), and who were admitted to the Nishi-Hiroshima Rehabilitation Hospital less than 3 months after suffering their stroke. Exclusion criteria included (1) history of major psychiatric illness (seven patients); (2) medical illness (four patients) or speech impediment (117 patients) that may affect cognitive function and ability to provide consent; (3) subarachnoid hemorrhage (25 patients); (4) physical disability which precludes cognitive testing (12 patients). The remaining 243 patients were included as subjects in this study.

CT findings

The study had a naturalistic design using 243 CT scans. As such a high sample size would not have been possible with MR, the CT technique used is adequate. CT scanning was performed on all patients at admission (with a follow-up CT scan every 1-3 months after admission). Damage to the basal ganglia or frontal lobe (including lacunar infarcts) was defined as a sharply demarcated hypodense lesion with a diameter >5 mm on CT. We classified patients into four groups according to the degree of basal ganglia or frontal lobe damage: no damage, damage to the left side only, damage to the right side only, and damage to the bilateral basal ganglia or frontal lobe. The measurement of the volume of CT-defined LDA was calculated according to the formula $0.5 \times A \times B \times C$; where A and B represent the largest perpendicular diameters and C is the thickness (Montaner et al. 2001).

Psychological assessment

We used the Japanese version of the SDS to examine the subjective severity of affective depression (Yamaguchi et al. 1992) and used a Japanese version of the apathy scale (AS) to quantify the apathetic state (Yamagata et al. 2004). We classified the patients into two groups according to their test scores: a non-depressed group (SDS score < 45 points) and a depressed group (SDS score ≥ 45 points), and a non-apathetic group (apathy score < 16 points) and an apathetic group (apathy score ≥ 16 points). The cut-off point was determined on the basis of a previous report on Japanese stroke patients (Yamaguchi et al. 1992).

Statistical analyses

Different degrees of basal ganglia or frontal lobe damage (none, left only, right only and bilateral) were compared with SDS or AS scores by one-way analysis of variance (ANOVA) followed by a post-hoc Fisher protected least significant difference test (Fisher PLSD test). Values were considered to be significant at $P < 0.05$. The Stat View 5.0 (SAS Institute, Inc., Cary, NC) statistical package was used for all analyses.

Results

Baseline structures and the frequency of PSD in all patients

The subjects consisted of 162 males and 81 females (age: 65.2 ± 11.3, past history of stroke: 27 cases (11.1%), time interval between onset and admission: range 7–90 days, mean 40.7 ± 19.6 days). SDS and AS scores over the cut-off limits were observed in 79 (32.5%) and 98 (40.3%) patients, respectively. Of these, 50 patients (20.6%) showed elevation of both SDS and AS, therefore 126 patients (51.9%) were found to have affective and/or apathetic PSD.

The effects of lesion location on affective and/or apathetic PSD

Computed tomography densities of left side and cortical lesions (especially middle cerebral arterial territory damage; e.g., temporal lobe) were found to be greater in speech impaired patients (excluded from this study) than in other patients.

The severity of affective or apathetic PSD was related to CT-defined lesion volume (Mann–Whitney U-test, $P < 0.02$), consistent with a previous report (Nys et al. 2005). But no association could be demonstrated between severity of PSD and lesion location involving supra-or infra-tentorial LDA (Mann–Whitney U-test, $P > 0.2$), so further examinations were made of supratentorial stroke lesions in the frontal lobe and basal ganglia.

The SDS score increased significantly from none, right side only, left side only, to bilateral frontal lobe damage ($P = 0.0450$, ANOVA test) (Fig. 1). Post-hoc testing (Fisher's test) showed a difference between no damage and damage to the left side only ($P = 0.0237$). However, we did not find significant differences in AS scores in relation to frontal lobe damage.

The AS score increased significantly from none, left side only, right side only, to bilateral BG damage ($P = 0.0061$, ANOVA test) (Fig. 1). Post-hoc testing (Fisher's test) showed a difference between no damage and bilateral BG damage ($P = 0.0024$), and between left side only and bilateral BG damage ($P = 0.0075$). However, we did not find significant differences in SDS scores in relation to BG damage.

Discussion

We found that the severity of affective depression (SDS score) was associated with left frontal lobe damage, but not damage to the basal ganglia. Apathetic depression (AS score) was not related to frontal lobe damage but was related to damage to the basal ganglia in both the right and left hemispheres.

Although there is conflicting evidence as to whether the risk of depression after stroke is influenced by the location of the brain lesion, several explanations can be proposed for our findings. Soares and Mann (1997) suggested that functional abnormalities in frontal, subcortical, and limbic structures appear to be part of the pathophysiology of depression. Robinson et al. (1984) and Starkstein et al. (1987) exam-

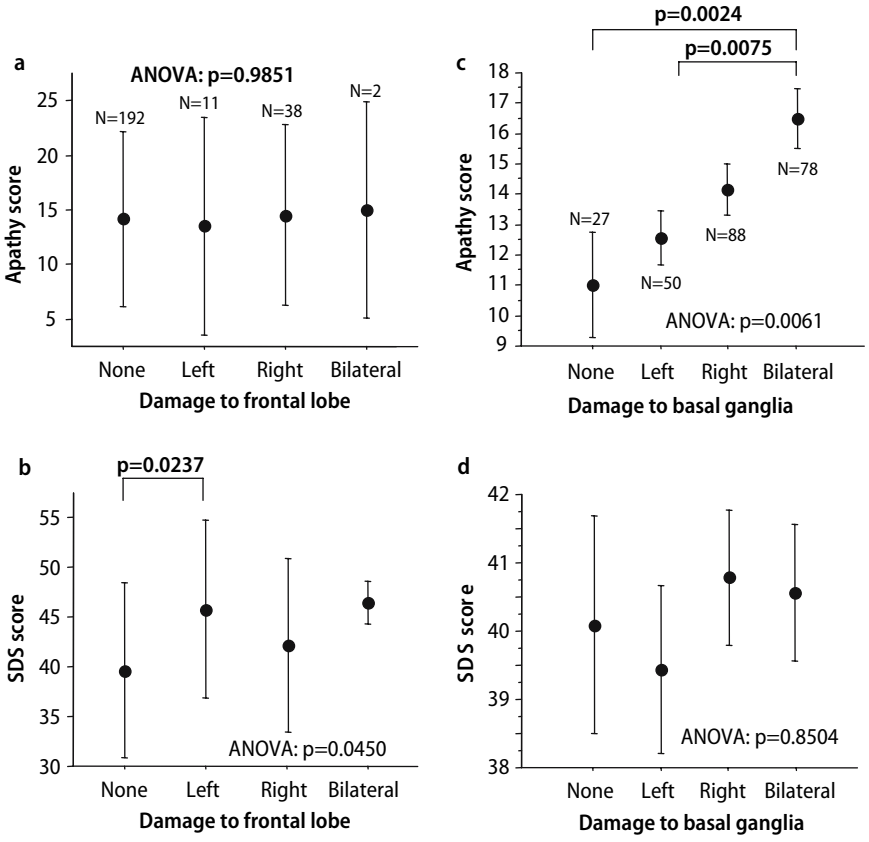

Fig. 1 Differences in apathy score (**A**, **C**) and SDS score (**B**, **D**) between patients with no damage, left side only, right side only, and bilateral damage to the frontal lobe (**A**, **B**) or basal ganglia (**C**, **D**). The midpoint, top and bottom of each vertical line represent the mean, upper, and lower 95% CI values, respectively. ANOVA of the four frontal lobe or basal ganglia damage subgroups shows significant results for SDS (**B**) or AS (**C**). The Fisher PLSD test also indicates that these parameters can distinguish between some of these SDS or AS subgroups, with the *P*-values given

ined depression in stroke patients using SDS, and their findings suggested a strong correlation between the severity of depression and proximity of the lesion to the frontal pole. Other studies also noted a significant association between strokes affecting the frontal lobe (or anterior part) of the left hemisphere and PSD (Alexopoulos et al. 1997). These reports agree with our findings that "depressed mood (affective PSD)" is associated with the left frontal lobe.

Starkstein et al. (1993) suggested that apathy was significantly associated with lesions involving the posterior limb of the internal capsule. Later, Yamagata et al. (2004) examined the relationship between apathy after subcortical stroke and neural orienting response to novel events using an event-related evoked potential technique, suggesting that apathy after subcortical (include basal ganglia) stroke is intimately linked to dysfunction of the frontal-subcortical system. These findings agree with our data, indicating that damage to basal ganglia leads to dysfunction of the frontal-subcortical system, resulting in apathy after stroke.

Several methodological limitations of this study should be acknowledged. First, patients with severe comprehension deficits and/or severe speech impediments, who had different lesion patterns compared to the other patients, were excluded from the study. Therefore, the results of this study may be biassed. Second, patients enrolled in this study only underwent CT scanning (not MRI). Thus, the presence of lesions that could not be visualized by CT may have influenced our findings. Third, we used a self-report questionnaire to measure the level of depression. Thus, the absence of objective assessment may have influenced our findings.

In summary, this study found that after a stroke there are two separate core symptoms ("depressed mood" or "loss of interest") with different underlying neuroanatomical mechanisms. Therefore, in order to help patients gain independence, future studies should examine whether these different lesion correlates of affective or apathetic PSD, separately or together, may also be reflected in different patterns of treatment response.

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