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Post-stroke fatigue is associated with impaired processing speed and memory functions in first-ever stroke patients

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ABSTRACT

Objective: Fatigue is a common consequence of stroke that frequently co-occurs with depression. Data on the cognitive associations of post-stroke fatigue (PSF) is scarce. We investigated the relationship of PSF with depressive symptoms and cognitive functioning after stroke.
Methods: One hundred and thirty-three working-aged patients with first-ever ischaemic strokes underwent neuropsychological and clinical assessment and evaluation for PSF and depressive symptoms at three months, six months, and two years after stroke. Cognitive domains evaluated included processing speed, memory, executive functions, and reasoning. Fatigue and depressive symptoms were assessed with subscales of the Profile of Mood States.
Results: Patients (mean age: 54 ± 9.5 years, 64.7% male) were divided into groups with ($n = 33$) and without ($n = 100$) PSF at three months after stroke. Patients with PSF at three months after stroke had slower processing speed at three months ($p = 0.003$) and six months ($p = 0.013$) after stroke and worse memory performance at six months ($p = 0.003$) after stroke than patients without PSF. Fatigue was also associated with more depressive symptoms. Impairments in processing speed at 3 months and memory at 6 months after stroke persisted after the depressive symptoms were controlled for. PSF was related to a lower rate of returning to work two years after stroke ($p = 0.046$).
Conclusion: PSF at three months after stroke is associated with depressive symptoms and negative cognitive and work-related outcomes following stroke. Deficits in processing speed and memory in patients with PSF were partly observed even after depressive symptoms were controlled for.

Introduction

The prevalent outcomes of stroke include cognitive dysfunction, depressive symptoms, and fatigue. The majority of first-ever stroke patients suffer from cognitive impairment [1]. Post-stroke cognitive deficits can affect post-stroke functional outcomes; however, accurate data on neuropsychological stroke outcomes remain scarce [2]. As many as one in two stroke patients suffers from depressive symptoms [3], and the prevalence rates for fatigue in stroke patients range from 25% up to 75% [4,5].

Post-stroke fatigue (PSF) has a potential negative impact on the patients' ability to return to work [6] and can interfere with their participation in rehabilitation programs [7]. Additionally, PSF is associated with cognitive functioning: it has been linked to impaired information processing speed in other neurological conditions, e.g. traumatic brain injury (TBI) [8] and multiple sclerosis (MS) [9]. Regarding stroke, however, the relationship between fatigue and cognitive impairment has received less attention. A relationship between PSF and the mini-mental state examination (MMSE) [10] has not been established [11–14]. However, the MMSE is a screening instrument for dementia with age-dependent scores, and it is not accurate in screening for cognitive deficits in stroke patients [15–17]. In a small study, stroke patients with PSF had impaired information processing speed compared to healthy controls [18]. To our knowledge, the only study of PSF and cognitive functioning using more extensive neuropsychological methods found attentional and executive dysfunction to be associated with PSF [19]. The direction of causality regarding PSF and cognitive dysfunction is still under debate, but it also has been suggested that cognitive impairment can affect fatigue [4,19].

Depressive symptoms frequently co-occur with PSF [20] and can cause cognitive dysfunction *per se* [3]. However, the possible impact of depressive symptoms on cognitive performance has generally not been accounted for in previous research [18].

In this study, we aimed to investigate the association of PSF with cognitive functioning and depressive symptoms after stroke in working-aged, first-ever stroke patients. Because the early identification of factors affecting recovery is critical, we focus on the consequences of PSF at three months after stroke and examine the relation

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between PSF at three months after stroke and both cognitive impairment and depressive symptoms at three months, six months, and two years after stroke.

Methods

Participants and study procedure

The patients are part of a larger cohort from two Finnish central hospitals including 230 consecutive patients aged 18–65 years with first-ever supratentorial ischemic strokes and Finnish as their native language. The exclusion criteria included any history of neurological or severe psychiatric disorders. All patients were treated according to clinical standards for stroke patients and underwent brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI). A control group of 50 healthy subjects, who met all the other inclusion and exclusion criteria but did not experience a stroke, was also assessed. This cohort has been partially described previously [21,22]. The Ethics Committee of the Helsinki University Central Hospital approved the study and consent procedure. Informed consent was obtained from all participants.

For this substudy, we included all patients who completed the neuropsychological assessments and questionnaire data at three months, six months, and two years after stroke. Seven patients with severe aphasia (the Aphasia Severity Rating Scale of the Boston Diagnostic Aphasia Examination [23] <4) at three months after stroke were excluded. Thus, the final study group included 133 patients.

Clinical data

The patients underwent a neurological examination at the acute phase and at six months after stroke. The stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) [24] at hospital admission and discharge. The patients' basic functional status was evaluated at the acute phase with the Barthel Index (BI) [25]. At the six-month follow-up, the NIHSS and BI were reassessed. A stroke neurologist (SM) visually evaluated the lesion location and the size and side of the infarct from CT or MRI. The infarct size was categorised as small (<1.5 cm), medium (1.5–4.0 cm), or large (>4.0 cm) by using a modified version of the Paciaroni *et al.* classification [26]. Relevant demographic and clinical data were obtained by interview and from medical records.

Cognitive assessment

A neuropsychological examination that evaluated four cognitive domains was completed at three months after stroke (mean 84.7 ± 23.9 days). *Processing speed* was evaluated with the Trail Making Test (TMT) form A [27,28], the Stroop colour naming subtask [29], and the Digit Symbol Coding subtest of the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) [30]. *Memory* was evaluated with the Logical Memory Test I of the Wechsler Memory Scale—Revised (WMS-R) [31], a 10-word list learning task [32], and an abbreviated version of the Benton Visual Retention Test [33]. *Executive functions* were assessed with a subtraction score of the TMT forms B and A, a subtraction score of the interference and naming subtasks of the Stroop test, and a phonemic fluency task [34]. *Reasoning* was assessed with the Similarities and Block Design subtests of the WAIS-III. The assessment was repeated at six months (mean 186.5 ± 13.2 days) and at two years (mean 737.9 ± 16.7 days) after stroke.

Data on fatigue, depressive symptoms, and return to work

The patients' fatigue and depressive symptoms were evaluated at three months, six months, and two years after stroke with a modified version of the Profile of Mood States (POMS) questionnaire [35]. This version of the POMS contains 38 adjectives that are rated on a 5-point Likert scale [36]. The fatigue (3 items) and vigour (6 items) subscales were used to assess fatigue. The fatigue subscale (POMS-F) has previously been established as a valid and feasible measure of PSF [37]. The vigour subscale (POMS-V) contains items that are closely related to fatigue (active, energetic, brisk, excited, vigorous, and alert) and was thus included in this study. The subscales had good inner consistency, with Cronbach's α of 0.86 for the fatigue subscale, 0.94 for the vigour subscale, and 0.90 for the combined subscales. The control group was assessed with the same questionnaire. To categorise PSF as being present, we used a cut-off of the 90th percentile level of the combined POMS-F and POMS-V subscales of the control group. Patients with higher scores than the cut-off were considered to have PSF.

Depressive symptoms were assessed with the depression subscale of the POMS (POMS-D; 7 items) at all time points. Clinically relevant depression was evaluated at two years after stroke with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [38]. A possible history of psychological disorders and psychopharmacologic medication was obtained at the acute phase.

Information on the patients' work status and possible changes in work load was collected at two years after stroke.

Statistical analysis

Differences in demographical and clinical data between the PSF and no-PSF groups were evaluated with the Mann–Whitney *U* test or the Chi-square (χ^2) test. The cognitive domains were analysed with multivariate analyses of variance and subsequent analyses of variance, and the POMS-D scores (3, 6, and 24 months after stroke) were used as covariates. The untransformed means are reported when transformations were used to obtain normality. The level of significance was set at $p < 0.05$. The Bonferroni correction was used in follow-up comparisons (univariate analyses). Bonferroni-adjusted *p* values are reported for univariate analyses. The data were analysed with SPSS version 19.0 (IBM Corp., Armonk, NY).

Results

Study cohort and course of PSF

The mean age of the patients ($n = 133$) was 54.6 ± 9.5 years, and 86 of the patients (64.7%) were male. The median NIHSS score was 2 (range 0–20) at hospitalisation and 1 (range 0–8) at discharge. At the acute phase, 100 patients (75%) had BI values of 100 (median 100, range 40–100).

From the cohort of 230 patients, the patients who were not eligible ($n = 97$) for this substudy were less educated (median 11 yrs., range 8–19 vs. 12, 9–20, $p = 0.001$) and had higher NIHSS scores at admission (median 3, range 0–24 vs. 2, 0–20, $p = 0.020$) and discharge (median 1, range 0–16 vs. 1, 0–8, $p = 0.042$) than the patients who were eligible for this substudy ($n = 133$). No significant differences in any other demographic or clinical variables or mood state and fatigue measurements were found between the eligible and ineligible patients at three months after stroke.

In this cohort, 50 patients (37.6%) were considered to have experienced PSF in at least one assessment, but the course of PSF varied somewhat (Fig. 1). Only 13 patients (9.8%) had PSF at all assessments.

In subsequent analyses, the group with PSF at three months after stroke ($n = 33$) was examined and compared with the group without PSF at three months after stroke ($n = 100$). These two groups did not differ in any essential demographic characteristics or acute stage stroke-related clinical variables (Table 1).

Depressive symptoms and PSF

The patients with PSF at three months after stroke reported more depressive symptoms in the POMS-D at three months ($p < 0.001$), six months ($p = 0.009$), and two years post-stroke ($p < 0.001$) than the patients without PSF (Table 2). Furthermore, at two years after stroke, the patients with PSF experienced more clinically relevant depression than the patients without PSF and reported significantly more symptoms of depressed mood ($p < 0.001$) and loss of pleasure ($p < 0.001$) in the SCID-I. Additionally, the patients with PSF reported significantly more changes in appetite or weight, insomnia or hypersomnia, psychomotor agitation or retardation, lack of energy, and difficulties in thinking or concentration (all $p < 0.05$) than the patients without PSF (Table 2).