Poststroke fatigue following minor infarcts

A prospective study

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ABSTRACT

Objective: To explore the potential relationship between fatigue following strokes and poststroke mood, cognitive dysfunction, disability, and infarct site and to determine the predictive factors in the development of poststroke fatigue (PSF) following minor infarcts.

Methods: Ninety-nine functionally active patients aged less than 70 years with a first, nondisabling stroke (NIH Stroke Scale score ≤6 in acute phase and ≤3 after 6 months, modified Rankin Scale score ≤1 at 6 months) were assessed during the acute phase and then at 6 (T1) and 12 months (T2) after their stroke. Scores in the Fatigue Assessment Inventory were described and correlated to age, gender, neurologic and functional impairment, lesion site, mood scores, neuropsychological data, laboratory data, and quality of life at T1 and T2 using a multivariate logistic regression analysis in order to determine which variables recorded at T1 best predicted fatigue at T2.

Result: As many as 30.5% of the patients at T1 and 34.7% at T2 (11.6% new cases between T1 and T2) reported fatigue. At both 6 and 12 months, there was a significant association between fatigue and a reduction in professional activity. Attentional-executive impairment, depression, and anxiety levels remained associated with PSF throughout this time period, underlining the critical role of these variables in the genesis of PSF. There was no significant association between the lesion site and PSF.

Conclusion: This study suggests that attentional and executive impairment, as well as depression and anxiety, may play a critical role in the development of PSF.

GLOSSARY

ACTH = adrenocorticotropic hormone; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **FAI** = Fatigue Assessment Instrument; **HARS** = Hamilton Anxiety Rating Scale; **HDRS** = Hamilton Depression Rating Scale; **MS** = multiple sclerosis; **NIHSS** = NIH Stroke Scale; **PSF** = poststroke fatigue; **TSH** = thyroid-stimulating hormone.

Pathologic fatigue is frequent in stroke patients (30%–72% of stroke patients) and is referred to as poststroke fatigue (PSF).[1–5] It may persist for a long time after the acute event and have detrimental influences on rehabilitation, survival, and on the patient's family, social, and professional life.[3] The correlates and mechanisms of PSF remain relatively underexplored compared with poststroke cognitive and affective changes. Following a stroke, fatigue can occur during activities requiring a sustained effort (fatigability) or be associated with other pathologies (anemia, cardiac insufficiency). However, it may present as primary PSF: a state specifically caused by focal brain dysfunction and characterized by a long-standing lack of effectiveness while executing any motor and mental tasks, independent of poststroke depression, significant cognitive or neurologic sequelae, or other clinical dysfunctions.[6–9]

Pathophysiologic studies[10–12] in postviral syndromes, multiple sclerosis (MS), and basal ganglia diseases suggest that primary PSF might be linked to damage to the reticular formation and the neural attentional network.

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This study aims to investigate the subjective dimension of PSF in the absence of significant sensory/motor impairment by exploring potential relationships between fatigue and poststroke mood, cognitive dysfunction, disability, and infarct site. To achieve this, we evaluated the patients (following nonsevere first stroke) longitudinally in order to obtain predictive neurologic, affective, and demographic factors for the development of fatigue. We also evaluated fatigue in 2 subgroups: nondepressed patients to better define the determinant of fatigue in the absence of depression and professionally active patients who were most likely to feel disabled by the presence of fatigue.[4,9]

METHODS

Patient selection. Subjects were prospectively recruited from patients examined consecutively in our department during the acute stage of a first ischemic or hemorrhagic stroke (<7 days of onset), and who were included in the Lausanne Stroke Registry.[13] The inclusion criteria consisted of 1) a "nondisabling" (minor) stroke, defined by total score on the NIH Stroke Scale (NIHSS) ≤6 at discharge from hospital and ≤3 after 6 months, Rankin score <1 at 6 months; 2) age ≤70 years; and 3) regular involvement in working activities (job, housework) before the stroke.

The exclusion criteria consisted of prior impairment in daily life activities, recurrent stroke, subarachnoid hemorrhage, TIA, psychiatric history, known sleep disorders, and coexisting diseases interfering with fatigue assessment (e.g., musculoskeletal diseases, MS).

Standard protocol approvals, registrations, and patient consents. We received approval from the local Ethical Committee on Human Experimentation. Written informed consent was obtained from all the participants. There was no conflict of interest in this study.

Acute phase assessment (<7 days from stroke onset). We recorded the patients' characteristics and stroke features according to the standard protocol of tests from the Lausanne Stroke Registry, including epidemiologic data, neurologic status, and brain imaging.[13] Subjects were categorized into 2 age groups (≤45 years and >45 years) and distributed in a statistically balanced manner. We also registered the professional status of each patient at the time of the stroke (i.e., professionally active, retired, no lucrative activity).

Anatomic data. Brain MRI (in 65 patients) or CT (in 34 patients) imaging was performed at the acute poststroke stage for each patient. Images were analyzed in a "blind" manner (i.e., without disclosing the patients' names). By means of anatomic templates, we differentiated the following anatomic regions: frontal, temporal, occipital, parietal, mesencephalic, basal ganglia, thalamic, centrum semiovale, and cerebellar. In some cases, lesions simultaneously affected 2 different areas (e.g., parietal and temporal); in these cases both areas were recorded. Thus the final total number of lesions is greater than the total number of patients. Patients were categorized into 5 groups according to their lesion site: cortical, subcortical, cortical-subcortical, cerebellar, and brainstem.

Chronic phase assessment: Fatigue, neurologic, neuropsychological, and emotional evaluation at 6- and 12-month follow-up (T1 and T2, respectively). The same protocol was administered at T1 and at T2. The patients were once again informed about the aims of the study before the T1 evaluation.

Instruments and scoring. Fatigue was assessed using the Fatigue Assessment Instrument (FAI),[14] a multidimensional, 29-item autoevaluation scale that allows the quantification of fatigue through a fatigue severity score (appendix e-1 on the *Neurology*® Web site at www.neurology.org).

Disabilities were evaluated using the modified Rankin Scale.[15] A neuropsychologist conducted a detailed cognitive examination. The following tests were used for different functions: Attention: phasic alert and divided attention[16] and D2.[17] Language: object naming from line drawing (French version of the Boston Naming Test)[18] and written comprehension (Boston Diagnostic Aphasia Examination). Executive functions: a modified version of the Stroop test[18]; category and letter fluency tasks, and a nonverbal directed fluency task (5 points). Short-term verbal and nonverbal memory: digit span and the Corsi blocks test.[18] Long-term memory: Rey auditory verbal memory task.[18]

Each test was rated dichotomously (normal vs abnormal, cutoff performance set at below 2 SD) according to a standardized neuropsychological battery.[18] For each domain (language, memory, attention, executive functions), the patient's score was considered abnormal if one of the scores was below 2 SD. Thus, a global cognitive score was developed internally, based on the percentage of tests (>10%) showing abnormal performances.

A psychiatrist performed the psychiatric evaluation. The Hamilton Depression Rating Scale (HDRS) and the Hamilton Anxiety Rating Scale (HARS)[19] criteria were fulfilled, and the diagnosis of a major depression was established according to *DSM-IV* criteria. HDRS and HARS scores were treated as continuous variables for most statistical analyses. To complete the analysis in the subgroup of nondepressed patients, the diagnosis of depression was applied to patients who met the *DSM-IV* criteria for major depression or in patients whose total HDRS score was ≥10, a value that has been frequently used as a cutoff in stroke populations.[20]

The assessment was completed by a measure of the quality of life (Stroke-Specific Quality of Life Scale),[21] data on plasma levels of cortisol in the morning, adrenocorticotropic hormone (ACTH), T_4 (free), and thyroid-stimulating hormone (TSH) and the recording of professional activity modifications following the stroke.

Statistics. ***Descriptive statistics.*** The sociodemographic characteristics, cognitive status, and FAI scores were presented for the 6- and 12-month evaluations. The fatigue severity was presented in terms of percentage of patients with fatigue severity scores of >4.[14,22] A general cognitive status was defined based on the percentage of tests showing abnormal performances.

Correlative analyses. The potential relationships between fatigue on the one hand and neurologic, neuropsychological, functional, emotional, and physiologic variables on the other were investigated at T1 and T2. Statistical analyses were carried out on the whole group, and separately on the 2 subgroups, "nondepressed patients" and "professionally active patients" (at the onset of the stroke).

While the FAI severity score was used as our outcome measure, the independent variables consisted of age, gender, changes in activity rate (for patients still in active professional life at onset

of stroke), neurologic and functional impairment, level of depression, degree of anxiety, lesion side and site, neuropsychological data, laboratory data, quality of life, and abulia. First, a univariate analysis was performed for each variable (one-way analysis of variance for categorical variables and linear regression model for continuous variables). Variables with a p value < 0.05 were kept for the final stepwise multiple regression analysis. Level of significance was set at 0.05.

We also used multivariate logistic regression analysis to determine which variables recorded at T1 best predicted T2 fatigue (later fatigue).

A statistician performed the analyses using Stata program.

RESULTS **Demographic data.** Over a continuous period of 2 years, out of a total number of 715 stroke patients admitted, 125 patients fulfilled the inclusion criteria upon discharge from the hospital. A total of 109 (87.2%) patients (37 women [34%] and 72 men [66%]) were evaluated at a 6-month follow-up (T1). Among the missing subjects, 2 had moved and could not be contacted, 10 refused the assessment, and 4 were excluded because of a NIHSS score outside the limits of inclusion criteria at the time of evaluation (at 6 months). At the 12-month follow-up (T2), 99 (79.2%) subjects (33 women [33%] and 66 men [67%]) completed the examination. Of the 10 dropout patients between T1 and T2, 3 had had a stroke recurrence, 1 had died, 3 were excluded because we diagnosed a sleep apnea syndrome, and 3 refused to continue the study.

Descriptive data. Table 1 shows sociodemographic characteristics, cognitive status, and scores on the FAI. Among the patients who reported fatigue at 6 months following a stroke, 77.3% still reported fatigue at the 12-month follow-up (30% at T1 and 23.2% at T2). The total percentage of patients reporting fatigue at the second follow-up was 34%. A significant number (11.6%) were new cases who only started to report fatigue later on (figure), which was mostly attributable to social changes, such as resuming work. Fatigue was rated as the worst symptom by 23% of the patients (n = 25) at T1 and by 25% (n = 25) at T2, and it was considered a new phenomenon (differing both qualitatively and quantitatively from fatigue experienced before the stroke) by 49.5% (n = 54) and 44.4% (n = 44) of patients at T1 and T2, respectively. When taking into account the patients involved in a professional activity at the time of their stroke ("professionally active" subgroup, n = 56), we observed that 64.3% (n = 36) had reduced or given up lucrative activity at the 6-month follow-up; the percentage decreased slightly to 55.4% (n = 31) at 12 months poststroke.

Concerning the cognitive functions, nearly one-third of the patients showed some impairment in global cognitive scores, i.e., had more than 10% abnormal or marginal performances when tested (table 1). Concerning stroke locations at the 6-month follow-up, we assessed 41 patients with lesions in the right hemisphere, 48 in the left, 3 with bilateral lesions, and 17 with lesions in the subtentorial area. At the 12-month follow-up, 38 patients had right and 39 had left hemispheric damage, 2 had bilateral lesions, and 20 had nonhemispheric strokes.

With respect to lesion sites, at T1 and T2 we found 29 and 27 with subcortical damage, respectively, 28 and 24 with cortical lesions, 22 and 20 with cortico-subcortical damage, 25 and 24 with brainstem lesions, and 5 cerebellar strokes.

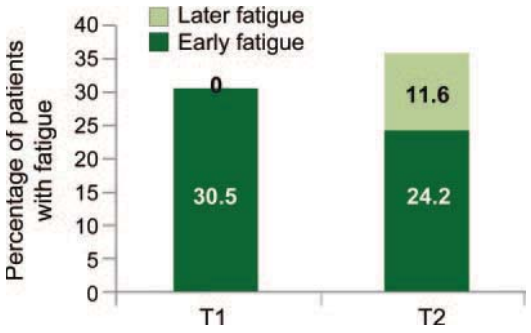
Regression analyses. At T1, the highest correlation coefficients were found for NIHSS, Rankin, HDRS, and HARS total scores, sustained attention, phasic alert, global cognitive scores, age, and modification of professional activity (reduction or suppression). At T2, the strongest correlation concerned HDRS, HARS, language, long-term memory, executive

Table 1 Sociodemographic characteristics, cognitive status, and FAI scores

	6 months	12 months
Sample size	109	99
Age, y, mean ± SD	51.1 ± 13.8	50.9 ± 14.1
Male, n (%)	72 (66)	66 (66.7)
Impaired cognitive function, n (%)[a]	33 (30.3)	34 (34.3)
Reduced professional activity, n (%)[b]	36 (64.3)	31 (55.4)
Mean ± SD FAI score	3.2 ± 1.8	3.3 ± 1.7
FAI score >4, n (%)	33 (30)	34 (34)

Abbreviation: FAI = Fatigue Assessment Instrument.
[a] Patients showing abnormal performances on more than 10% of the neuropsychological tests administered.
[b] Among patients involved in professional lucrative activity before the stroke.

Figure Percentage of patients with fatigue at T1 and T2



Early fatigue shows the fatigue that appeared at T1, and later fatigue shows the fatigue that appeared between T1 and T2.

logistic regression results for variables with 05

e	Odds ratio	*p* Value	95% CI
score (HARS)	1.331	0.000	1.161–1.527
score (HARS)	1.562	0.001	1.211–2.013
	0.431	0.043	0.191–0.972
score (HARS)	1.329	0.001	1.121–1.576
d activity	4.362	0.025	1.207–15.763
sion score (HDRS)	1.332	0.000	1.141–1.554
ed Attention	3.893	0.004	1.537–9.860
sion score (HDRS)	1.561	0.000	1.221–1.994
ve function	4.792	0.008	1.504–15.263
sion score (HDRS)	1.287	0.002	1.094–1.514
ed attention	3.318	0.019	1.121–9.069

ce interval; HARS = Hamilton Anxiety Rating Scale; HDRS = Scale.

functions, sustained attention, phasic alert, divided attention, global cognitive scores, and modification of professional activity. There was no correlation between infarct site and fatigue severity scores, except for a tendency toward left parietal lesions ($p = 0.086$). At T1, the multivariate analysis based on variables with a p value < 0.05 (table 2) revealed that severe fatigue (FAI > 4)[14,22] was independently associated with anxiety levels, as shown by the HARS score. When considering nondepressed patients, significant variables were younger age ($\leq$45) and anxiety levels, while in the "professionally active" group, severe fatigue was associated with anxiety levels and modification (reduction or suppression) of professional activity.

At T2 (1 year), severe fatigue was independently associated with higher depression scores (HDRS) and with sustained attention dysfunction. In nondepressed patients, the level of depression scores and impairment in executive functions constituted the relevant associated variables. In the "professionally active" group, the significant factors were higher depression scores (HDRS) and sustained attention deficit.

We did not find any statistically significant correlation between PSF and plasma levels of cortisol, ACTH, T_4 (free), and TSH. Moreover, no significant association between PSF and lesion side and site was found.

DISCUSSION In this study, our purpose was to characterize PSF longitudinally in the first year following the first minor strokes (NIHSS <6, Rankin score <1 at 6 months). Our data suggest that 1) fatigue is a frequent, stable, and persisting symptom following a nondisabling stroke, affecting 30% of patients at 6 months and 34% at 1 year after a minor infarct; 2) cognitive (attentional or executive) impairment and levels of depression and anxiety remain independently associated at T2, underlining the critical role of these 2 variables in the persistence of PSF; and 3) there is no clear association between fatigue and lesion site. Other factors, such as the high psychophysiologic cost of a delayed resumption of professional activity (>6 months), seem also to contribute to the lack of improvement in fatigue.

Using the FAI, we found a slightly lower incidence (or frequency) of PSF when compared to other studies.[1–4,22,23] As fatigue has also been correlated with functional impairment,[24] this might be explained by the fact that we included only minor strokes and "nondisabled" patients. In fact, stroke patients may experience increased energy demand during gait due to the inability to activate normal motor patterns; this may cause poor biomechanical efficiency and promote an earlier onset of fatigue.[23] Moreover, the male/female ratio in our group was high (66 M/33 F).[25] In addition, FAI severity subscores measure different aspects of fatigue (mental and motor fatigue, quality of fatigue, interferences with activities). Finally, other mechanisms, such as lower incidence of cognitive dysfunction[26] and differences in scale sensitivity, may explain these results.[27]

We found a remarkable stability of fatigue across time (mean FAI severity score of 3.2 $\pm$ 1.8 at the first evaluation [T1] and 3.3 $\pm$ 1.7 at the second [T2]; 30% of patients at T1 and 34% at T2 had FAI >4). Compared to the 6-month follow-up, 1-year self-rated fatigue remains unchanged despite significant improvement in neurologic and functional outcomes, as well as depression. Therefore, our data show that PSF is a stable symptom in the first year after a stroke. A stabilizing of fatigue frequency after the subacute period has been suggested by other longitudinal studies, as reported by 59% of patients at 10 days, and then by 44%, 38%, and 40% of stroke patients respectively at 3 months, 1 year, and 2 years following hospitalization for stroke.[28] Another longitudinal study[29] showed an increased percentage of self-rated fatigue between admission and the 6-month and 1-year follow-ups; fatigue was indeed reported by 51.5%, 64.1%, and 69.5% of patients, respectively. The Fatigue Severity Scale scores (a first and very similar version of the FAI severity score) increased from 4.1 to 4.5 and then 4.7 across time. In cross-sectional studies, the time elapsed since stroke was found to have no influence on the presence and severity of fatigue.[2,30]

Mood factors are closely related to fatigue (general or severe) at any time following a stroke. Paradoxically, anxiety and depression levels remain closely associated with fatigue when considering the nondepressed group, a finding described in other neurologic pathologies.[31] Until recently, fatigue after stroke was misleadingly regarded by some clinicians as a mere component of poststroke depression. While it has been shown that fatigue and depression are correlated,[3] it has become clear that poststroke depression and fatigue are commonly dissociated from each other.[9,32,33] Particularly, fatigue was also reported by many patients who did not have depressive moods,[34] a dissociation already highlighted in patients with Parkinson disease[35] or MS.[36] The question remains as to whether depression is sometimes a consequence rather than a factor of fatigue.[2,30]

PSF, which is classically expected to occur even in the absence of mental or functional impairment, seems positively associated with cognitive dysfunction.[26,37] In particular, 1 year after a stroke, severe fatigue was associated with sustained attention impairment and, in nondepressed patients, with executive dysfunction. Cognitive impairment has been found to affect fatigue after subarachnoid hemorrhage[38] and brain injuries,[39] but such association has received little attention after stroke. In a long-term study[40] no association between fatigue and cognitive impairment was found, but this could be explained by the fact that they used only the Mini-Mental State Examination, which does not assess attention or executive function.[e1] The direction of causality is a matter of debate, but we suggest that cognition may also directly affect fatigue: first, the symptom was present in both physically active and nonactive patients; second, at 12 months after stroke, the severity of fatigue was not correlated with a return to professional activities, which would have been more likely if it was the primary cause of cognitive dysfunction.

Conversely, we found no statistically significant associations between PSF and lesion site and side, functional and neurologic impairment, and what could be called localized cognitive dysfunction. The only trend that we found in univariate analyses was that of high fatigue severity scores in patients with left parietal lesions, but these were not significant. One reason could be the relatively few subjects, since lesion effects have been observed in larger groups.[7,40] However, the link between fatigue and brain lesions appears to be very complex. Like poststroke depression, PSF is a complex, heterogeneous phenomenon that cannot be easily explained by lesion localization. In fact, published studies,[1–4,e2,e3] together with some unpublished data, have shown that it is difficult to find definite predictors for PSF. Lesion location may only contribute to a small extent to the risk of developing PSF, which could be due to the multiplicity of fatigue expressions.[22] In fact, such clinical cohort analyses suggest that there are 2 different types of fatigue in stroke: a "task-specific" fatigue linked to cognitive or physical sequels (such as residual aphasia following left parietal lesions, when mental fatigue appears after speaking for a certain time), and a "primary" PSF linked to subtle attention difficulties after brainstem or subcortical strokes that impair the cortical activating system.[9]

There is still controversy over the correlation between lesion sites and PSF, but high depression scores and cognitive impairment (especially in the executive function and sustained attention domains) play important roles in the development of PSF.

AUTHOR CONTRIBUTIONS

N. Radman: writing the manuscript. F. Staub: executive work, evaluation of patients, statistics. T. Aboulafia-Brakha: statistics, figures, co-writing. A. Berney: psychiatric evaluation, participation in the design. J. Bogousslavsky: design, manuscript correction. J.M. Annoni: design, evaluation of patients, co-writing.

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DISCLOSURE

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