Poststroke fatigue and depression are related to mortality in young adults: a cohort study

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ABSTRACT
Objectives: To investigate the relationship between poststroke fatigue and depression and subsequent mortality in young ischaemic stroke patients in a population-based study.

Design: A prospective cohort study.

Setting: All surviving young ischaemic stroke patients living in Hordaland County.

Participants: Young ischaemic stroke patients aged 15–50 years at the time of the stroke were invited to a follow-up on average 6 years after the index stroke. Psychosocial factors and risk factors were registered. Fatigue was self-assessed by the Fatigue Severity Scale (FSS). Depression was measured by Montgomery-Åsberg Depression Rating Scale (MADRS).

Intervention: No intervention was performed.

Primary and secondary outcome measure: Mortality on follow-up.

Results: In total, 190 patients were included. The mean age on follow-up was 48 years and subsequent follow-up period was 12 years. Cox regression analysis showed that mortality was associated with FSS score (p=0.19) after adjusting for age (p=0.06) and sex (p=0.10). Cox regression analysis showed that mortality was associated with MADRS score (p=0.006) after adjusting for age (p=0.10) and sex (p=0.11).

Conclusions: Both fatigue and depression are associated with long-term mortality in young adults with ischaemic stroke. Depression may be linked to higher mortality because of psychosocial factors and unhealthy lifestyles whereas the link between fatigue and mortality is broader including connection to diabetes mellitus, myocardial infarction and psychosocial factors.

Outcome after ischaemic stroke is better among young adults than older patients. However, several studies have reported high long-term mortality in young adults with ischaemic stroke as compared to matched controls. Factors such as hypertension, alcoholism, coronary heart disease, severe stroke and age have been linked to mortality in young adults with ischaemic stroke.

The study of stroke among young people is important for several reasons. The aetiology of stroke is much more diverse and risk factors for stroke differ between young and old patients and may indicate separate approaches as to treatment. Stroke in young adults provides an opportunity to study stroke in general because of less comorbidity than in old patients. Fatigue has been recognised as a disabling symptom in non-depressed stroke patients. Young stroke patients need information on prognosis, including factors related to fatigue or depression, to make informed choices about vocation and employment. Among old stroke patients it has been shown that both fatigue and depression are associated with mortality. However, little is known about the effect of fatigue or depression on survival in young adults with ischaemic stroke.

We present data on the effect of fatigue and depression measured on an average 6 years after the index stroke and subsequent...
mortality. We hypothesised that fatigue and depression are associated with increased mortality in young adults with ischaemic stroke irrespective of stroke severity.

**METHOD**

All patients 15–49 years old with first-ever cerebral infarction from 1988 to 1997 living in Hordaland County were included in a database. An upper limit of 49 years was chosen because these patients have low comorbidity compared with that among older patients and because they still have many years left in the work force. Cerebral infarction was defined in accordance with the Baltimore-Washington Cooperative Young Stroke Study Criteria comprising neurological deficits lasting more than 24 h because of ischaemic lesions or transient ischaemic attacks where CT or MRI showed infarctions related to the clinical findings. We excluded patients with cerebral infarction associated with other intracranial diseases such as subarachnoidal haemorrhage, sinus venous thrombosis or severe head trauma. Case-finding was performed retrospectively as described previously.

Surviving patients were invited to a follow-up investigation in person in our out-clinic department on an average 6 years after the index stroke. On follow-up, data on employment, level of education and marital status were obtained by the authors. Risk factors including alcoholism, smoking, diabetes mellitus and myocardial infarction were registered. Stroke severity was determined by the modified Rankin Scale (mRS), Barthel Index (BI) and Scandinavian Stroke Scale (SSS) on follow-up. Cognitive function was assessed using the Mini-Mental State Examination (MMSE).

Fatigue was measured by the Fatigue Severity Scale (FSS). FSS is a nine-item questionnaire that assesses the effect of fatigue on daily living. Each item is a statement on fatigue that the subject rates from 1, ‘completely disagree’ to 7, ‘completely agree’. Examples of the items in the questionnaire are: ‘Fatigue is among my three most disabling symptoms’, ‘Exercise brings on my fatigue’ and ‘I am easily fatigued’. The average score of the nine items represents the FSS score (the minimum score being 1 and maximum 7). Fatigue was defined as FSS score ≥5.

Depressive symptoms were quantified using Montgomery-Åsberg Depression Rating Scale (MADRS) at the follow-up. Poststroke depression (PSD) was defined as MADRS score ≥7.

Subsequent survival state was registered by examining the official population registry by 1 August 2011. The study was approved by the local Ethics committee.

**Statistics**

Fisher’s exact test (categorical variables), Student t test (continuous variables) and pair-wise correlation test were used as appropriate. Cox regression analyses were used for disclosing variable associated with mortality. Kaplan-Meier survival curves grouped by dichotomised FSS (FSS<5 vs ≥5) and MADRS scores (MADRS<7 vs MADRS≥7) were obtained. All tests were two sided. Level of significance was set at p<0.05. STATA V.11.0 was used for analyses.

**RESULTS**

A total of 232 patients had first-ever ischaemic stroke. At the time of invitation 209 patients were alive and the present study includes 190 patients: 81 (43%) female patients and 109 (57%) male patients. The mean age on follow-up was 48 years. During a subsequent mean follow-up time of 12.4 years 32 (16.8%) patients had died. (The mean total follow-up time since the index stroke was 18 years.)

Univariate analyses showed that mortality was associated with factors such as being unmarried, unemployed, alcoholism, diabetes mellitus, myocardial infarction, age, mRS, SSS, BI, MMSE, FSS and MADRS scores (table 1).

Cox regression analysis showed that mortality was associated with FSS (HR=1.4, CI 1.1 to 1.7, p=0.005) after adjusting for age (p=0.06) and sex (p=0.19). Including BI, mRS or SSS separately did not change these findings. Figure 1 shows Kaplan-Meier survival curves dichotomised for FSS<5 and ≥5.

Cox regression analysis showed that mortality was associated with the MADRS score (HR=1.06, CI 1.02 to 1.11, p=0.006) after adjusting for age (p=0.10) and sex (p=0.11). Including BI, mRS or SSS separately did not change these findings. Figure 2 shows Kaplan-Meier survival curves dichotomised for MADRS<7 and ≥7.

**Table 1** Characteristics of young ischaemic stroke patients according to survival or death

|                  | Dead, n (%) | Alive, n (%) | p Value |
|------------------|-------------|--------------|---------|
| Total            |            |              |         |
| Male patients    | 22 (20)     | 87 (80)      | 0.17    |
| Female patients  | 10 (12)     | 71 (88)      |         |
| Unmarried        | 13 (27)     | 36 (73)      | 0.05    |
| Higher education | 8 (14)      | 48 (86)      | 0.67    |
| Unemployed       | 22 (29)     | 53 (71)      | <0.001  |
| Alcoholism       | 6 (55)      | 5 (45)       | 0.004   |
| Smoking          | 17 (22)     | 60 (78)      | 0.12    |
| Diabetes mellitus| 7 (35)      | 13 (65)      | 0.05    |
| Myocardial infarction | 10 (53)  | 9 (47)       | <0.001  |

**Mean (SD) Mean (SD)**

|                  | Mean (SD) | Mean (SD) |
|------------------|-----------|-----------|
| Age on follow-up | 51.2 (6.6) | 47.2 (8.3) | 0.01 |
| mRS score        | 1.7 (1.1)  | 1.3 (1.0)  | 0.03 |
| SSS score        | 54 (8.4)   | 56 (4.5)   | 0.08 |
| BI               | 96 (13)    | 99 (5)     | 0.04 |
| FSS score        | 4.9 (1.6)  | 4.0 (1.6)  | 0.003|
| MADRS score      | 7.8 (7.3)  | 4.3 (5.9)  | 0.004|
| MMSE             | 28.8 (3.6) | 28.2 (2.1) | 0.003|

BI, Barthel Index; FSS, Fatigue Severity Scale; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; SSS, Scandinavian Stroke Scale.
Stepwise Cox regression analyses based on all variables in table 1 showed mortality to be associated with alcoholism (HR=5.3, p=0.001), myocardial infarction (HR=3.0, p=0.011) and unemployment (HR=2.9, p=0.013) after adjusting for age (p=0.29) and sex (p=0.28).

Stepwise Cox regression analyses based on all variables in table 1 excluding alcoholics showed mortality to be associated with diabetes mellitus (HR=3.1, p=0.023), myocardial infarction (HR=4.1, p=0.001) and MADRS score (HR=1.08, p=0.002) after adjusting for age (p=0.32) and sex (p=0.36) (see table 2).

Tables 3 and 4 show correlation analyses between MADRS and FSS scores and relevant factors. MADRS was correlated with smoking, alcoholism, being unmarried, unemployment and stroke severity (all p<0.05). FSS was correlated with diabetes mellitus, myocardial infarction, alcoholism, unemployment, depression and stroke severity (all p<0.05). Correlation was the highest between MADRS scores and FSS scores (r=0.60, p<0.001). There was moderately high correlation between FSS scores and unemployment (r=0.31, p<0.001).

The main findings in the present study were that both fatigue and depression were associated with subsequent long-term mortality irrespective of stroke severity. Consistent with these findings other studies have disclosed that fatigue is associated with mortality in older stroke patients.15 16 Likewise others have reported depression to be associated with mortality in older stroke patients.6 17–19 It is unlikely that fatigue causes death. It is more probable that fatigue is linked to other factors that directly cause death. Consistent with this, fatigue disappeared in the stepwise Cox regression analyses including all variables associated with death on univariate analyses. We found a strong correlation between fatigue and depression. Weaker correlations were found between fatigue and mRS, unemployment, alcoholism, diabetes mellitus and myocardial infarction. Studies including older stroke patients reported poststroke fatigue to be associated with diabetes mellitus and myocardial infarction.15 20 Both diabetes mellitus and myocardial infarction are diseases associated with mortality in young adults with ischaemic stroke.1 It seems likely that the link between fatigue and diseases such as diabetes mellitus and myocardial infarction partially explains the

| Table 2 Cox regression survival analysis among non-alcoholic young adults with ischaemic stroke |
|-----------------------------------------------|---------|---------|
| Age                                           | 1.04    | 0.97 to 1.1 | 0.32 |
| Sex                                           | 1.5     | 0.6 to 3.4  | 0.36 |
| Diabetes mellitus                             | 3.1     | 1.2 to 8.3  | 0.023|
| Myocardial infarction                         | 4.1     | 1.8 to 9.4  | 0.001|
| MADRS score                                   | 1.08    | 1.03 to 1.13 | 0.002|

MADRS, Montgomery-Åsberg Depression Rating Scale.

| Table 3 Montgomery-Åsberg Depression Rating Scale (MADRS) and correlation analyses in young ischaemic stroke patients[colcnt=3] |
|-----------------|---------|---------|
| Age             | 0.05    | 0.49    |
| Female patients | 0.07    | 0.31    |
| Diabetes mellitus| 0.08   | 0.27    |
| Myocardial infarction | 0.01 | 0.90   |
| Smoking         | 0.15    | 0.04    |
| Alcoholism      | −0.17   | 0.02    |
| Married         | −0.20   | 0.007   |
| Employed        | −0.31   | <0.001  |
| Higher education| −0.12   | 0.11    |
| FSS score       | 0.60    | <0.001  |
| mRS score       | 0.14    | 0.05    |
| MMSE            | −0.08   | 0.25    |

FSS, Fatigue Severity Scale; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; MADRS, Montgomery-Åsberg Depression Rating Scale.
The strengths of this study are the population-based approach and the long-term follow-up period. A weakness is that patient finding was performed retrospectively which may have affected both case finding and case ascertainment. Another weakness is that we have no data on the cause of death or the use of antidepressive medication. Risk factor profile and stroke treatment have changed since 1988–1997, and this should be taken into account while interpreting the results.

In conclusion, both fatigue and depression are associated with long-term mortality in young adults with ischaemic stroke. Depression may be linked to higher mortality because of psychosocial factors and unhealthy lifestyles whereas the link between fatigue and mortality is broader including connection to diabetes mellitus, myocardial infarction and psychosocial factors.

**Contributors** HN and HN conceived the idea of the study and were responsible for the design of the study. HN was responsible for undertaking the study analyses and produced the table and the graphs. The initial draft of the manuscript was prepared by HN and then examined by HNy for critical revision. HN and HNy were responsible for the acquisition of the data and both contributed to the interpretation of the results. Both authors read and approved the final manuscript.

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