

**SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY  
(PhD)**

**Post-stroke depression: Long-term prospective study in the Hungarian  
population**

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**UNIVERSITY OF DEBRECEN**

**DOCTORAL SCHOOL OF CLINICAL MEDICINE**

**DEBRECEN, 2021**

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The PhD defense will be held on 7 December, 2021 at 1.30 p.m.

Live online access will be provided via Zoom. If you wish to join the discussion, please send an e-mail to the [rberecz@med.unideb.hu](mailto:rberecz@med.unideb.hu) address until 12.00 p.m. at latest on the previous day of the defense (6 December 2021). For technical reasons after that deadline, it will be not possible to join the defense.

## **Introduction**

Cerebrovascular disorders and depression are the leading causes of disability worldwide. The relationship between stroke and depression can be examined epidemiologically from two perspectives: does depression increase the risk of stroke; and what is the frequency of depression after cerebrovascular incident.

This essay focuses on the frequency and predictors of depressive mood disorders after stroke and the role of post-stroke depression (PSD) in case fatality in the Hungarian population.

The relationship between stroke and mood disorder was described by Kraepelin as early as 1910. Depending on the study method (definition of depression, study population, tests used in the study, the timing of assessments), the reported rate of post-stroke depression varies between 1.5% and 78%. Data available from several studies showed that PSD was present in about 30% of stroke patients within a month after stroke, 1–6 months, and 6 months to 1 year, and 25% more than 1 year, respectively. In follow-up studies with periods between 1 and 5 years after a stroke, the cumulative incidence of PSD ranged between 39-52%. Nevertheless, PSD remains unrecognised and untreated in many cases. Several investigators have reported that PSD was associated with poor recovery in activities of daily living, reduction of in rehabilitation treatment efficacy, cognitive and functional recovery, a higher risk of recurrent stroke, and increased case fatality risk. Furthermore, depressive mood after stroke has a negative effect on personal relationships and quality of life.

Many different predictors of PSD were investigated across previous studies. Disability after stroke, cognitive impairment, stroke severity, history of pre-stroke depression, anxiety, lack of family/social support, and left anterior location were reported as predictors of depression after stroke in previous reviews.

A systematic review and meta-analysis of studies found increased/early case fatality at follow-up for individuals with PSD. It seems that the relationship between depression and fatal outcome after stroke is related to the follow-up duration. The short-term studies (<2 years) did not show a statistically significant association between depression after stroke and case fatality; the medium term (2-5 years) follow-ups showed results above the threshold of statistical significance and the analysis of long-term investigations (>5 years) showed some trend.

Depression may affect the prognosis and risk of case fatality after stroke because stroke patients suffering from depression may be less adherent to treatment. Depression is associated with poor health behaviours (i.e. smoking, physical inactivity, poor diet, lack of medication compliance),

which have a negative impact on survival. Furthermore, depression is related to other major comorbidities, such as diabetes, hypertension, neuroendocrine changes (e.g., sympathetic nervous system activation, dysregulation of the hypothalamic-pituitary-adrenocortical axis), platelet aggregation dysfunction, and immunological, inflammatory changes.

The pathogenesis of PSD is multifactorial: hereditary and psychosocial factors, decreased level of monoamines, increased neuroinflammation, abnormal neurotrophic response, interleukin-6 (IL-6), and Brain Derived Neurotrophic Factor (BDNF) may be involved.

The recommended screening tools for PSD are the Hamilton Depression Rating Scale (HDRS), the Beck's Depression Inventory (BDI), the Center for Epidemiologic Studies Depression Scale (CES-D), Patient Health Questionnaire with 9 items, (PHQ-9), and the Montgomery-Åsberg Depression Rating Scale (MADRS).

## **Aims**

The aims of the present study were:

1. Assessment of the prevalence of post-stroke depression in a Hungarian patient population in the acute and chronic stages of stroke.
2. To investigate the role of the patient's gender, age; location, type, and severity of stroke; as well as the degree of functional impairment and the possible role of history of depression in the development of post-stroke depression.
3. To analyse the presence and severity of depressive symptoms in stroke patients in acute stage as well as 4 years after stroke, and to test whether the severity of depressive symptoms is an independent predictor of case fatality during 18 years following the index stroke.

## **Patients and methods**

During a 4-month period from September 1995 to January 1996, patients with acute ischemic or haemorrhagic stroke were consecutively included in the study within one week after admission to our stroke unit. Written informed consent was obtained from all patients. To quantify the severity of stroke, we used the Scandinavian Neurological Stroke Scale (SNSS), the Orgogozo scale (ORG), and the Barthel index (BI) in the acute stage. The severity of depressive symptoms was evaluated by the 13 items version of the Beck Depression Inventory (BDI) and the Hamilton Rating Scale for Depression (HDRS). The examination for the study was scheduled for the seventh  $\pm$  2 day after admission. Exclusion criteria were transient ischemic attack, disturbance of the level of consciousness (somnolence, stupor, or coma), severe aphasia or dementia that prevented reliable evaluation of the mood with the applied scales. Patients who died or were discharged before the planned day of examination were also not included.

At four years after stroke, the same investigator contacted the patients at their home and re-evaluated them personally.

Survival status and date of death were checked from medical records at 18 years after stroke.

Descriptive statistical analysis was used to characterise the distribution of the severity of depressive symptoms. Normality of the parameters was checked by Kolmogorov-Smirnov test. We used the Spearman correlation to evaluate the association between initial stroke severity, age and the severity of depressive symptoms 4 years after stroke. Initial and 4-year values for scale scores were compared by the Wilcoxon matched-pairs test, and the association of initial and 4-year score values were evaluated by the Spearman correlation coefficient. Kaplan-Meier curves were constructed, and the log-rank tests were used to compare the survival distributions between patient groups. The general linear model was used for multivariate analysis to identify independent predictors of the length of survival.

The Kruskal-Wallis analysis of variance (ANOVA) by ranks was used to test whether lesion location had a significant effect on scores.

Statistica for Windows v.11 (StatSoft, Tulsa, USA) was used for statistical analysis. Values are expressed as mean  $\pm$  standard deviation (SD). Differences were considered statistically significant at  $p < 0.05$ .

## Results

During the period of the study, 190 patients were admitted to the ward with acute cerebrovascular disease. Of these, 19 died and 42 were discharged before the scheduled examination day of the study. Ten patients had transient ischemic attacks, while disturbance of level of consciousness (N=6 patients), severe aphasia (N=17), dementia (N=7), or lack of cooperation (N=7) were exclusion conditions for further 31 patients from the study. The 82 remaining patients with acute stroke had a mean age of 65.8 years. No significant differences were found between men and women in any of the parameters. Comparing these 82 patients with the 108 who were excluded from the study, we found that those who were excluded were on average four years older, did not have significantly more severe stroke signs on admission, however, their hospital case fatality was significantly higher than that of the study group.

Adjustment disorder with depressed mood (Beck score  $\geq 5$ ) was diagnosed in 22 patients (27%) in the acute stage. 19% of patients had at least 10 points on the Beck scale (clinically moderate depression), and less than 5% of patients scored at least 15 (severe depressive symptoms). Of the 82 patients, 79 had computed tomography (CT) scans. In our patient group, the severity of post-stroke depression did not depend on age, gender, or lesion location. A significant correlation between the severity of stroke and depressive symptoms was found.

There were 48 survivors (59%) at 4 years and 13 survivors (16%) at 18 years after stroke. At the follow-up stage 4 years after stroke, scores on the stroke scales as well as on depression scales correlated with both stroke and depressive scores of the acute phase, and more severe strokes were associated with more severe depressive symptoms also 4 years after stroke.

The severity of depressive symptoms either in the acute phase or 4 years after stroke was not an independent predictor of the length of survival within the period of 4-18 years after stroke. Due to the strong effect of stroke severity, gender (male), and age on survival, there was only a trend towards an association between the severity of depressive symptoms after stroke and case fatality. However, a subgroup of patients with moderate or severe depression at 4 years had a significantly shorter post-stroke survival.

## Summary

Cerebrovascular diseases are associated with a high incidence of psychiatric disorders. Depressive illness after stroke has been increasingly studied during the last three decades. Post-stroke depression is estimated to occur in 30% of the patient during the first year after stroke. Numerous studies have given information on prevalence, pathogenesis, clinical course, treatment, and prevention. Despite this high level of comorbidity, depressive symptoms appear to remain frequently unrecognised and untreated. This has a negative effect on rehabilitation, quality of life, cognitive function, and the mortality of stroke patients.

During a 4-month period from September 1995 to January 1996, 190 patients with acute ischemic or haemorrhagic stroke were consecutively admitted to the Stroke Unit of the Department of Neurology, Medical School of Debrecen. Of these patients, 82 were eligible to be included in our study within one week after admission and 41 after 4 years in the follow-up investigation. There were 13 survivors at 18 years.

Major results:

Adjustment disorder with depressed mood was diagnosed in 22 patients (27%) in the acute stage ( $7\pm 2$  days after stroke). Although the prevalence of PSD was slightly lower in our study than expected from the former reviews, our results do not differ significantly from the data found in the international literature.

In our patient group, the severity of post-stroke depression did not depend on age, gender, or lesion location. We found a significant correlation between the severity of stroke and depressive symptoms.

At 4 years after stroke, scores on the stroke scales as well as on depression scales correlated with both stroke and depressive scores in the acute phase and we found that more severe strokes were associated with more severe depressive symptoms 4 years after stroke.

The severity of depressive symptoms either in the acute phase or 4 years after stroke is not an independent predictor of the length of survival within the period of 4-18 years after stroke. Due to the strong effect of stroke severity, gender (male), and age on survival, there was only a trend towards an association between the severity of depressive symptoms after stroke and case fatality. However, a subgroup of patients with moderate or severe depression at 4 years had a significantly shorter post-stroke survival.



Nyilvántartási szám: DEENK/288/2020.PL  
Tárgy: PhD Publikációs Lista

Jelölt: Kellermann Mónika  
Doktori Iskola: Klinikai Orvostudományok Doktori Iskola  
MTMT azonosító: 10070204

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**A közlő folyóiratok összesített impakt faktora: 27,038**

**A közlő folyóiratok összesített impakt faktora (az értekezés alapjául szolgáló közleményekre):  
4,176**

A DEENK a Jelölt által az iDEa Tudóstérbe feltöltött adatok bibliográfiai és tudományometriai ellenőrzését a tudományos adatbázisok és a Journal Citation Reports Impact Factor lista alapján elvégezte.

Debrecen, 2020.10.14.

