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# POST-STROKE DEPRESSION

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SUMMARY – Depression following a stroke, also referred to as post-stroke depression (PSD), has long been recognized as one of the most common complications of stroke. PSD has significant adverse consequences on the recovery of motor and cognitive deficits, as well as on the risk of mortality associated with stroke. The prevalence of PSD varies over time with an apparent peak 3-6 months after stroke and subsequent decline reaching about 50% of the initial rates at one year. The natural course of major depression after stroke has spontaneous remission typically 1 to 2 years after stroke. However, it has also been observed that depression becomes chronic and may persist for more than 3 years following stroke. On the other hand, minor depression appears to be more variable, with both short term and long term depression occurring in these patients. Early recognition of PSD symptoms and introduction of pharmacological treatment is of great importance in the reduction of stroke complications and stroke mortality as well as for better functional outcome.

Key words: *Stroke – complications; Stroke – psychology; Depression – etiology; Depression – drug therapy; Depression – prevention and control*

## Introduction

In the acute stage of stroke, there is an important change in sensorimotor interactions with both internal and external world; it is so called 'modified mental processing'. Up to one third of stroke patients have 'modified mental processing'. Such patients have no, or only poor, memory of what actually happened during the acute stage of stroke; it usually occurs without specific damage to the classic anatomical structures involved in memory processing[1]. Another phenomenon, called anosognosia or poor recognition of the neurologic deficit, can be present in the acute stage of stroke. Therefore, post-stroke depression (PSD) needs to be distinguished from emotional lability (sometimes referred to as post-stroke emotionalism or catastrophic reactions). Post-stroke emotionalism is reported in about 10% of stroke patients; it is an abnormal lability of mood during which the patient laughs or cries for no evident reason, suffers anxiety, apathy and loss of psychic self-activation (athymhormia). Typically, the patient does not feel the expected emotion associated with this outward reaction[2-4].

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## Epidemiology

Prevalence rates of PSD range from 30% to 50%; in four community-based studies 31.8% (range 30%-44%), in studies carried out in acute hospitals 25%-47%, and in studies conducted in rehabilitation centers 35%-47%[5].

The occurrence of PSD peaks three to six months after stroke. In a study on 100 patients followed for 18 months, the symptoms of PSD occurred in 46% of patients in the first two months, whereas only 12% of patients experienced their first symptoms 12 months

after their stroke. Major depression and minor depression are the most frequently recognized manifestations of PSD. The course of PSD can be rather lengthy, for example, symptoms of major depression identified in 27% of stroke patients persisted for approximately one year, whereas symptoms of minor depression lasted for more than two years in 20% of stroke patients.

## Clinical Manifestations

The clinical manifestations of PSD are similar to those of idiosyncratic late onset depression, referred to as vascular depression identified in patients that may have overt or silent stroke(s) after age 65 or subcortical bilateral white matter ischemic disease. The symptoms of vascular depression consist of mood abnormalities, neuropsychological disturbances with impairment of executive functions, greater tendency to psychomotor retardation, poor insight and impaired activities of daily living. Vegetative symptoms consisting of disturbances of sleep, libido and level of energy were significantly more common in depressed than in non-depressed stroke patients at initial evaluation, and at 3, 6, 12 and 24 months. The prevalence of major depression in four community-based studies ranged from 11% to 15%, in studies carried out in acute hospitals from 10% to 27%, and in studies conducted in rehabilitation centers from10% to 40%. The prevalence of minor depression in four community-based studies was 8%-12%, in studies carried out in acute hospitals 11%-20%, and in studies conducted in rehabilitation centers 21%-44%[6-10].

The most frequently used scale for evaluating depression in stroke patients is the Hamilton Depression Rating Scale (HDRS); in the literature, the General Health Questionnaire (GHQ), Hospital Anxiety and Depression Scale (HAD), Aphasic Depression Rating Scale (ADRS), or some modified scales such as the Lausanne Emotion in Acute Stroke Study (LEASS) can also be found in the literature. In the evaluation of neurologic deficit and functional state, the National Institute of Health Stroke Scale (NIHSS), Rankin Scale and Barthel Index are most frequently used, whereas the Mini Mental State Exam (MMSE) and Montreal Cognitive Assessment (MoCA) are most widely employed for evaluation of cognitive functions[11].

There is a bidirectional relationship between stroke and depression; there is a high prevalence of depression in stroke patients and a higher risk of stroke in depressed people (3.36 relative risk), even when other conventional stroke risk factors (hypertension, diabetes, hyperlipidemia, heart disease and tobacco use) are under control (2.67 relative risk)[12]. Eriksson *et al.* demonstrated a previous stroke to be a risk factor for PSD (OR 1.25; 95% CI, 1.12-1.38), whereas the Lausanne Emotion in Stroke Study found no statistical significance (3/2 studies)[13]. Starkstein *et al.* showed the patients with major PSD to have significantly more cognitive deficits than non-depressed patients having experienced a similar location and size of the left hemisphere stroke; however, this did not apply to strokes in the right hemisphere[14,15].

The various risk factors associated with PSD include stroke location and size, temporal relation between PSD and stroke, and the size of the ventricles. Clinical studies showed patients with stroke in the middle cerebral artery territory to have longer duration of PSD symptoms (82% had symptoms at 6-month follow up, and 62% at 12- and 24-month follow up), in comparison to patients with posterior circulation strokes (20% at 6-month follow up, and 0% at 12- and 24-month follow up). Robinson *et al.* report that there is so called anterior to posterior gradient, which is different according to the hemisphere involved, being posterior to anterior for the left hemisphere and anterior to posterior for the right hemisphere. Bogousslavsky *et al.* showed PSD to be in strong correlation with lesions in the subcortical white matter, thalamus, basal ganglia and brain steam, rather than cortical lesions with specific cortical disturbance. Starkstein *et al.* compared the magnitude of subcortical atrophy in brain CT studies obtained immediately after stroke. Patients that developed PSD had a significantly greater degree of atrophy at this stage than those that did not[14-19].

There is a higher frequency of left than right strokes in PSD patients if the symptoms develop in the first 10 days; the relationship disappears if the onset of symptoms takes place 3 months after stroke. If the symptoms appear 1 year or later after stroke, right sided lesions are more frequent. Overt sadness is more frequently associated with left than with right lesions (86% *vs.* 61%; $P<0.05$). Crying is also more frequent in left than in right lesions (50% *vs.* 20%; $P=0.02$). With right-side lesions, anosognosia is clearly associated with neglect (95% *vs.* 34% for neglect *vs.* no

neglect; $P$=0.01). Regional cerebral blood flow values can also be useful in PSD prediction. Temporal lobe hypoperfusion (lower cerebral blood flow (CBF) values in mesial temporal cortex) may reflect dysfunction of the limbic system and be critical for the occurrence of depressive symptoms in patients with subcortical stroke. Patients with lower CBF in the left frontal or right parieto-occipital regions were more depressed in comparison with those with other brain lesions[16-20].

When symptoms of depression appear more than one year after stroke, right side lesions are more frequent. Stroke severity and disability may cause a reactive depressive process in the early stages after stroke, but probably do not mediate the development of PSD in the long term. There is a significantly higher prevalence of PSD among patients with non-fluent aphasia, but not in patients with fluent aphasia. The presence of PSD has been found to have unfavorable impact on the recovery of cognitive function, recovery of ability to perform activities of daily living and on the risk of mortality[21]. Large prospective studies have reported poorer functional outcome at 15 months in patients with depression 3 months after stroke and a strong correlation of functional outcome and depressive symptoms at both 3 months and 1 year after stroke. Depression after stroke led to 3.4-fold increase in mortality up to 10 years after stroke. Mood symptoms on a self reported rating scale were associated with 12- and 24-month mortality after stroke (OR 2.4; 95% CI, 1.3-4.5 and OR 2.4; 95% CI, 1.4-4.1, respectively). DESTRO study showed that depressive symptoms were more severe in patients with earlier onset, with no appreciable difference between those diagnosed between the first and sixth month; they were less severe in cases with later development of depression ($P$<0.05). In multivariate analysis, male patients had a 3 times higher probability than female patients of good autonomy in both stair climbing and activities of daily living (OR=3.32; 95% CI, 1.67-6.18 and OR=2.92; 95% CI, 1.63-5.42, respectively). Female patients had a higher risk of walking with a cane (OR=1.69; 95%, CI 1.04-2.76) or of partial autonomy with respect to activities of daily living (OR=1.90; 95%, CI 1.25-2.91). Difference in functional outcome might be due to different approaches to their disabilities, with women showing greater insecurity. DESTRO study found a higher frequency of women (35.39% without and 48.56% with PSD; $P$<0.001)[22-27]. FINNSTROKE study showed an older age to be an independent predictor of PSD. Eriksson *et al.* found younger age to be a predictor of PSD[13]. DESTRO study found no statistical significance; these results are still controversial. Meta-analysis showed no statistical significance between the age and PSD (13 of 17 studies in Hackett and Anderson). Twenty percent of stroke patients will make no recovery, and 60% will make complete recovery. On evaluating recurrent stroke there must be information on previous disability: activities of daily living dependent (11.6% *vs.* 7%; OR 2.69; 95% CI, 2.44-0 2.97), living alone (54.8% *vs.* 45.3%; OR 2.42; 95%, CI 2.18-2.69)[29-31].

## Therapy and Prevention of Post-Stroke Depression

The aim of PSD treatment is to achieve complete symptom remission of the depressive episode, which may have favorable impact on recovery of neurologic deficits[32,33]. The efficacy of pharmacotherapy of PSD has been investigated in several studies with tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Kimura *et al.* showed that responders to treatment with antidepressant medication had higher MMSE scores compared with placebo[33]. Gianotti *et al.* compared recovery of motor deficit and disability in PSD patients treated with antidepressant medications *versus* placebo (treated patients were significantly more likely to achieve symptom remission)[34]. Prevention with sertraline (50-150 mg/day) was investigated during one year in a double blind study; 8.3% of treated patients developed PSD as compared with 22.8% of patients on placebo ($P$=0.037)[35]. Robinson *et al.* showed the patients treated with nortriptyline to have an increased likelihood of survival at six years (61% *vs.* placebo 34%). Nortriptyline (100 mg/day) showed significant improvement in comparison with fluoxetine (40 mg/day) and placebo[36]. In a double blind study of fluoxetine (20 mg/day) *versus* placebo, Fruehwald *et al.* showed that patients on treatment and placebo experienced comparable improvement during the first 4 weeks, by 12 weeks patients on fluoxetine continued to improve, while those on placebo experienced recurrence of symptoms[37]. Citalopram and nortriptyline double blind studies failed to show improvement of cognitive deficits even in the presence of depression improve-

ment. It is important to recognize and diagnose depression after stroke. This is not only because of the increased suffering depression causes to patients that already have much to cope with, but because depression after stroke is associated with worse prognosis and there is evidence that pharmacological treatment substantially improves this outlook[38-40].

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Sažetak

## DEPRESIJA NAKON MOŽDANOG UDARA

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Depresija koja se javlja nakon moždanog udara jedna je od češćih komplikacija istog i ima značajan utjecaj na oporavak motoričkog i kognitivnog oštećenja, pa tako i na smrtnost od moždanog udara. Učestalost depresije koja se razvija nakon moždanog udara je promjenjiva uz povećanu pojavnost 3-6 mjeseci nakon moždanog udara, te izrazitu regresiju nakon godinu dana za oko 50%. Velike depresivne epizode koje se javljaju nakon moždanog udara spontano regrediraju nakon godinu do dvije, u težim slučajevima depresija može prijeći u kronični oblik koji traje tri i više godina. Pojavnost manjih depresivnih epizoda nakon moždanog udara jako varira te je njihova prevencija i liječenje individualno. Rano prepoznavanje simptoma depresije koja se javlja nakon moždanog udara te uvođenje specifične farmakološke terapije od velikog je značenja za smanjenje komplikacija i smrtnosti od moždanog udara te za poboljšanje funkcionalnog oporavka.

Ključne riječi: *Moždani udar – komplikacije; Moždani udar – psihologija; Depresija – etiologija; Depresija – terapija lijekovima; Depresija – prevencija i kontrola*