DEPRESSION AND PSYCHOLOGICAL DISTRESS AS RISK FACTORS FOR STROKE AND WORSE STROKE RECOVERY: CLINICAL IMPLICATIONS AND THERAPEUTIC OPTIONS

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ABSTRACT

Stroke and depression have a strong bidirectional association: on the one hand, depression and psychosocial distress are well known risk factors for stroke; on the other hand, stroke is known to be a strong risk factor for depression. In the first 2 years after a stroke approximately one-third of patients suffer from a post-stroke depression (PSD). PSD aggravates the burden of physical, psychological, and social disability after stroke, and hinders patient participation in rehabilitation. PSD is associated with a poorer outcome and increased mortality. For the treatment of PSD, selective serotonin reuptake inhibitors (SSRIs) were recommended. Interestingly, SSRIs also have positive effects on motor recovery in stroke patients even without depression, but may increase vascular risk.

Keywords: Depression, stroke, psychosocial stress, selective serotonin reuptake inhibitor (SSRI), prevention.

INTRODUCTION

Each year approximately 16 million people worldwide suffer a first ischaemic stroke. About one-third of these people remain disabled.1 In addition to the well-established risk factors, various studies and meta-analyses during the last years have demonstrated that both depression and psychosocial distress were both independent risk factors for ischaemic stroke. During the first 2 years after stroke, up to 30% of patients developed depression, known as post-stroke depression (PSD). PSD aggravates the burden of physical, psychological, and social disability after a stroke and hinders patient participation in rehabilitation. In these patients, selective serotonin reuptake inhibitors (SSRIs) were recommended. However, less is known about whether the treatment of depression leads towards a better outcome. This paper overviews recent studies concerning the bidirectional association between risk of depression in stroke patients as well as depression and psychosocial distress as risk factors for stroke. Moreover, new treatment options in stroke patients and preventing strategies for PSD are described. For this review we searched the PubMed databases and screened references for the items: “stroke”, “depression”, “psychosocial distress”, and “selective serotonin reuptake inhibitor”. Only reviews, original articles, and meta-analyses published in English were included.

DEPRESSION, PSYCHOSOCIAL DISTRESS, AND STROKE

Depression is a Risk Factor for Stroke

Depression is known to increase the risk of stroke.2 Data from the Framingham Heart Study analysing 4,120 patients demonstrated that the risk of stroke...
in patients younger than 65 years was 4.2-fold higher in persons with depressive symptoms, even after adjustment for education and other risk factors; in participants older than 65 years this association could not be detected. A large meta-analysis of 17 studies with >200,000 patients determined the association between stroke risk and depression. After adjustment for various risk factors the relative risk of stroke was 1.43 (95% CI: 1.17-1.54), without a significant sex difference. Another systematic review and meta-analysis included 28 prospective cohort studies with a follow-up between 2 and 29 years and described an overall hazard ratio (HR) of 1.45 (95% CI: 1.29-1.63) for total stroke in depressive patients. Jackson et al. recently observed a >2-fold higher risk (odds ratio (OR): 2.41, 95% CI: 1.78-3.27) of stroke in women between the age of 47 and 52 years without a history of stroke during a follow-up of 3 years. After adjustment for several risk factors such as socioeconomic status, lifestyle, and physiological factors the OR was 1.94 (95% CI: 1.37-2.74).

**Chronic Psychosocial Stress and Stroke Risk**

Surtees and colleagues found in 20,627 stroke-free participants, aged 41-80 years, that increased psychological distress is associated with elevated stroke risk. Episodic major depressive disorder was not associated with incident stroke in this study. A large population-based trial in Sweden analysed chronic psychosocial stress and long-term outcome, cardiovascular morbidity, and mortality in middle-aged men. The OR for cardiovascular events in patients with chronic psychosocial stress was 1.27 (95% CI: 1.15-1.39). Even after adjustment for various risk factors, the difference remained statistically significant. The highest risk was found for fatal stroke in men with an OR of 2.04 (95% CI: 1.07-3.88). According to the results of the INTERSTROKE study both depression and psychosocial distress are risk factors for stroke. This international multicentre study performed in 22 countries defined psychological distress as at least several periods of general stress at work or at home in the past year. Egido et al. observed a gender-independent increased stroke risk in stroke patients with stressful habits and type A behaviour. Henderson et al. analysed the risk of stroke mortality and incident stroke in relation to psychological distress in a population-based cohort in Chicago, including 4,120 persons with a medium age of 77 years and a follow-up of about 6 years. Four psychosocial indicators (depressive symptoms, perceived stress, neuroticism, and life satisfaction) measured psychological distress. The authors found a strong association between psychological distress and stroke mortality even after adjustment for stroke risk factors. Distress was strongly associated with haemorrhagic strokes (HR: 1.0, 95% CI: 1.28-2.25) but not with ischaemic stroke.

**Incidence of PSD**

The incidence of PSD varies between 25-36%. A recent study analysed the prevalence, incidence, and predictors of depression in a cohort of stroke patients older than 75 years up to 10 years after stroke. The main finding of this hospital-based cohort of survivors of first or recurrent ischaemic stroke was a remaining high prevalence of depression up to 10 years. Moreover, the baseline geriatric depression score was the main predicting factor for depressive symptoms after stroke at all time points. Cognitive impairment was a significant univariate predictor of depression up to 4 years of follow-up. In the first year after stroke, previous stroke and number of vascular risk factors were also predictors for depression. Ayerbe et al. analysed the incidence of PSD in patients registered in the South London Stroke Register between 1995 and 2009 (n=4022 at registration) during a follow-up of 15 years. The authors found a cumulative incidence of 55% and prevalence ranging from 29-39% in their population. Interestingly most episodes of depression started within a year after stroke. Overall, 33% occur within the first 3 months after stroke and none 10 years after stroke. Main predictors for depression in this population were disability, pre-stroke depression, cognitive impairment, stroke severity, and anxiety. A recently published systematic review found that the most frequently cited risk factors were sex (female), history of depression, stroke severity, functional impairments, level of independence, and family/social support.

**Prevention of PSD**

In the literature, different strategies were discussed to prevent PSD. Palomäki et al. studied the effect of 60 mg mianserin or placebo in a double-blind controlled study for 1 year after acute ischaemic stroke in 100 consecutive patients. They did not find that early initiation of antidepressant therapy is able to prevent PSD. However, the rate of depressive patients was low in the study population, which might have affected the results.
Robinson et al.\(^6\) described that the use of escitalopram or problem-solving therapy resulted in a significantly lower incidence of depression over 12 months of treatment compared with placebo in non-depressed patients with recent stroke. In an intention-to-treat analysis, problem-solving therapy did not achieve significant results over placebo. Rasmussen et al.\(^7\) tested the effect of sertraline in the prevention of PSD. 137 non-depressed patients after experiencing an acute ischaemic stroke were randomly assigned to 12 months of double-blind treatment with either sertraline (n=70) or placebo (n=67). Sertraline was significantly better than placebo. Only 10% of the sertraline-treated patients developed depression, compared to 30% of the placebo group. Another study described 0.45-0.73). Recently, Lawrence et al.\(^21\) reviewed the association between post-stroke SSRI use and outcome in a nationwide prospective score-matched follow-up study. Patients treated with SSRI had a lower risk of myocardial infarction (MI) and recurrent stroke. For the combined endpoint stroke and MI, the difference in both groups was significant with a HR of 0.77 (95% CI: 0.62-0.96). SSRI use after stroke was associated with increased mortality, which might reflect a combination of uncontrolled confounding by interaction owing to the underlying depression and an increased bleeding risk.\(^27\) According to the results of a large meta-analysis of 52 studies using SSRI in stroke, participants receiving SSRI were more likely to have gastrointestinal side-effects, seizures, and bleedings.\(^30\)

**outcome of Patients with PSD**

PSD is associated with poorer functional outcome.\(^22\) Moreover, the rehabilitation efficacy and the activity of daily living were reduced in depressed patients.\(^23\) Besides advanced motor function disabilities, depressed stroke patients are more likely to be cognitively impaired.\(^24\) Studies have shown that PSD increases the mortality rate at 1 year following a stroke.\(^25\) Some trials observed that depression increases the risk of first and recurrent stroke by 45% to 80%.\(^26,27\) In a systematic review and meta-analysis including 13 studies and more than 59,000 patients, the OR for mortality after stroke was 1.22 (95% CI: 1.02-1.47) in depressive stroke patients.\(^28\) In studies with a follow-up shorter than 2 years, no significant association between death and depression after stroke was found. In studies with >5 years of follow-up a trend was detected. Studies with a duration between 2 and 5 years after stroke reached statistical significance. A multi-centre prospective cohort study in China including 2,306 patients with acute stroke showed a 49% increase in OR of recurrent stroke at 1 year in patients with PSD, compared to patients without PSD following a stroke (OR: 1.49, 95% CI: 1.03–2.15). There was no significant correlation between anti-depressant drugs and the risk of recurrent stroke at 1 year following a stroke (OR: 1.96, 95% CI: 0.95–4.04).\(^29,30\)

**SSRI in Stroke Patients**

A systematic Cochrane review found that antidepressant medications are effective in treating PSD.\(^31\) Today, SSRRIs are the recommended pharmacotherapy of PSD due to their favourable tolerability profile. However, antidepressive medication in elderly stroke patients might increase the risk of haemorrhagic or ischaemic stroke due to an interaction with antiplatelet agents.\(^32-35\) A recent meta-analysis found that the use of SSRI was associated with a 1.48-fold increased risk of ischaemic stroke and a 1.3-fold increased risk of haemorrhagic strokes.\(^36\) Mortensen et al.\(^37\) studied the association between post-stroke SSRI use and outcome in a nationwide prospective score-matched follow-up study. Patients treated with SSRI had a lower risk of myocardial infarction (MI) and recurrent stroke. For the combined endpoint stroke and MI, the difference in both groups was significant with a HR of 0.77 (95% CI: 0.62-0.96). SSRI use after stroke was associated with increased mortality, which might reflect a combination of uncontrolled confounding by interaction owing to the underlying depression and an increased bleeding risk.\(^27\)

**Improvement of Motor Function with SSRI**

A small study including eight stroke patients demonstrated that a single dose of fluoxetine is able to improve motor performance.\(^38\) A few other small studies using SSRI in stroke patients suggested that this drug might have positive effects.\(^39-41\) Functional magnetic resonance imaging (MRI) revealed an activation of the ipsilesional
insular and lateral motor cortex 5 hours after application of 20 mg fluoxetine. According to these positive results, a double-blind placebo-controlled trial in patients with ischaemic stroke with haemiparesis or haemiplegia was initiated in nine stroke centres in France. 118 patients were randomly assigned to 20 mg fluoxetine or placebo and the motor recovery in these patients was compared using the Fugl-Meyer motor scale score (FMMS). The FMMS improved significantly after 3 months in the fluoxetine group (mean: 34 points, 95% CI: 29.7-38.4) versus 24.3 points (95% CI: 19.9-28.7, p=0.003; Table 1). The main adverse events in the fluoxetine and placebo groups were hyponatraemia, transient digestive disorders including nausea, diarrhoea, and abdominal pain, hepatic enzyme disorders, psychiatric disorders, insomnia, and partial seizure. In conclusion, fluoxetine significantly improves motor function in stroke patients without depression after 3 months, and occurrence of depression was lower in the fluoxetine group. Another multicentre, randomised, placebo-controlled trial found that 10 mg escitalopram per day prevents the development of PSD and was associated with improved short and long-term memory recovery. Experimental studies described a neurogenic and neuroprotective effect of SSRI. A meta-analysis of all published and non-published randomised controlled trials with SSRI (52 studies and 4,059 patients) given within the first year after stroke to determine the effect on dependency, disability, and other clinical outcomes was performed by Mead et al. The age of the patients

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Table 1: Overview of prospective placebo-controlled studies analysing the motor recovery in patients after ischaemic stroke using selective serotonin-reuptake inhibitors.

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HSS: Hemispheric Stroke Scale; NIHSS: National Institutes of Health Stroke Scale; FMMS: Fugl-Meyer motor scale score.

<table>
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<tr>
<th>Drug and treatment</th>
<th>Number of patients with SSRI</th>
<th>Number of patients in the control group</th>
<th>SMD and 95% CI</th>
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<tr>
<td>Fluoxetine</td>
<td>394</td>
<td>339</td>
<td>0.68 (0.31-1.06)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>65</td>
<td>65</td>
<td>1.38 (0.99-1.76)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>108</td>
<td>104</td>
<td>1.07 (-0.26-2.39)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>149</td>
<td>144</td>
<td>1.31 (0.67-1.95)</td>
</tr>
<tr>
<td>Total</td>
<td>691</td>
<td>652</td>
<td>0.91 (0.60-1.22)</td>
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Table 2: Standardised mean difference (SMD) and 95% confidence interval (CI) in the disability score after treatment with selective serotonin-reuptake inhibitors (SSRIs) in different randomised controlled trials including 1,343 stroke patients (according to Mead et al.44).
ranged from 55-77 years. The effect of treatment with SSRI versus placebo was greater in trials recruiting people with depression compared to people without depression at randomisation. In this meta-analysis SSRIs were effective in treatment of stroke patients even without depression (Table 2).

**CLINICAL IMPLICATIONS**

The lifetime incidence of depression is about 16% in the general population. For the treatment of depression, SSRIs were recommended as first-line treatment. However, the use of these drugs might increase the risk of ischaemic and haemorrhagic stroke. On the other hand, depression and psychosocial stress were independent predictors for ischaemic stroke. Moreover, about one-third of stroke patients developed a PSD, which implicates worse outcome and an increased risk for stroke recurrence. Therefore a systematic screening for depression after stroke should be performed after stroke onset. Due to the reduced length of hospital stay after stroke, the diagnosis of depression might be complicated. Man-van Ginkel et al. established a PSD prediction scale, which could help to identify stroke patients with a high risk of PSD. Other predictors for PSD were extent of stroke-related disability, pre-stroke depression, cognitive impairment, stroke severity, and anxiety.

Recently, a large amount of studies described a better clinical and functional outcome after stroke using SSRIs even in non-depressed patients. However, the evidence available in different studies does not provide a clear picture regarding the treatment of PSD and the efficacy and safety of SSRIs. Therefore, more placebo-controlled studies, including SSRIs but also non-medical therapies for PSD and functional outcome, are necessary. Moreover, potential side-effects such as increased bleeding risk, cardiac complications, and an increased risk of seizures should be taken into account.

**REFERENCES**