DEPARTMENT OF NEUROPSYCHIATRY

POST-STROKE DEPRESSION: A BRIEF REVIEW

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The association of neuro-psychiatric disorders with cerebro-vascular diseases has been recognized for centuries, but it is only within past 30 years that systemic studies have been conducted. Depressive disorders both major and minor, are probably the most common emotional disorders associated with CVA[1] Stroke patients with PSD suffer higher mortality rates and show a minor improvement in rehabilitation programs in comparison to non-depressed stroke patients. Consequently, they have worse functional outcomes and quality of life.

Incidence and Prevalence of PSD

The frequency of PSD has been studied in many countries of the world. The most-quoted studies of prevalence and incidence of PSD have utilized meta-analysis to create large databases. The most recent meta-analysis of 61 cohorts including 25,488 patients reported that 31% of patients developed depression at any time point up to 5 years following stroke. A prior meta-analysis of 43 studies published in 2013 included 20,293 patients and reported that the pooled prevalence of PSD was 29% at any time point within 5 years following stroke. In addition, the investigators found that the cumulative percent of patients who developed one or more depressions within the first 5 years following stroke ranged from 39% to 52%.[2]

The contributions by Ayerbe et al[3] and Hackett and Pickles [4] are significant because they

1. established that poststroke depression is a frequent and important complication of stroke and
2. refute prior assertions that the frequency of PSD has been exaggerated.

However, these meta-analyses have included many studies that have defined PSD based on arbitrary cut-off scores on a depression rating scale. These scales provide information about the frequency and severity of depressive symptoms, but their use as a diagnostic instrument has rarely been validated. On the other hand, it has been clearly established that the existence of depression should be ascertained based on a structured mental state examination and should meet established diagnostic criteria for a specific depressive disorder. Thus, these meta-analyses did not distinguish major depression from other forms of depressive disorders occurring after stroke, and many did not examine the time since stroke, the clinical setting (e.g., community or hospitalized patients), or the severity of stroke, all of which may affect the prevalence of depression.

On the basis of world literature Robinson calculated prevalence of depression across various clinical settings [2].Community-dwelling patients have the lowest prevalence rates; in this setting, 14% of patients present major depression, and 9%, minor depression. In hospital settings, including acute-care patients and those in rehabilitation, prevalence rates of major and minor depression were 21.6% and 20.0%, respectively. Among patients discharged from hospital, prevalence rates of major and minor depression were 24.0% and 23.9% at times ranging from 3 months to 3 years after stroke.

Etiology

The available evidence supports PSD as being multifactorial in origin, and consistent with the biopsychosocial model of mental illness. Nonetheless, the stroke itself poses the risk of depression. Stroke survivors are more predisposed to PSD compared to physically ill patients with similar levels of disability, even quite a long time after the stroke, regardless of other risk factors.

The risk factors that have been examined in the literature include genetic factors, age, gender, medical and psychiatric history, type and severity of stroke, lesion location, degree of disability, and social support.

a. Genetic factors. Common genetic variations might confer vulnerability or resilience to develop psychiatric illness when an individual faces an unusual stressful challenge. A few candidate genes have been examined as risk factors for PSD. The 5-HTTLPR and the STin2 VNTR polymorphisms of the serotonin transporter gene (SERT) have been associated with PSD in stroke survivors. Epigenetic modifications of 5-HTTLPR have also been implicated in the onset and severity of PSD In addition, among the same group of stroke patients, higher brain-derived neurotrophic factor (BDNF) gene methylation status was associated with incident PSD and more severe symptoms at 12 months follow-up.

b. Demographic factors. A systematic review of 21 studies of stroke patients reported that gender was not a significant risk factor for PSD. Age was not associated with PSD in 16 of these 21 studies. These findings were replicated in a review of 23 studies including 18,374 stroke patients.

c. Medical and psychiatric history. Major cardiovascular risk factors such as hypertension and hypercholesterolemia appear to have no relation to PSD. However, patients with PSD might be more likely to have a history of diabetes mellitus. A personal history of depression or anxiety or both was also consistently identified as a risk factor for PSD. A family history of depression was associated with PSD in the few studies that examined this association.

d. Stroke characteristics and lesion location. The available evidence strongly suggests a significant association between stroke severity and PSD. On the other hand, recent

systematic reviews argue against an association between PSD and the type (i.e., ischemic or hemorrhagic) or mechanism (i.e., thrombotic, embolic, etc.) of stroke.

Lesion location has been extensively investigated as a risk factor for PSD. The findings, however, have been inconsistent. Utilizing separate populations of patients in 1984 and 1987, two studies led by Robinson reported that acute stroke patients with left frontal or left basal ganglia lesions had a significantly higher frequency of major or minor depression than patients with other lesion locations. Furthermore, both studies found a significant correlation between the distance of the anterior border of ischemic lesion from the left frontal pole and severity of depression for both cortical and subcortical. Subsequent analysis by this research group found that the association of PSD with left frontal and left basal ganglia lesions appears to be a transient phenomenon restricted to the first 2 months following stroke, and the correlation of depression severity with distance of the anterior border of the lesion from the frontal pole in the left hemisphere remains significant only during the first 6 months after a stroke. However, subsequent metaanalysis of data from stroke patients who were either acute or chronic and had one or more stroke lesions reported no significant association with lesion location. The most recent and largest meta-analysis analyzed 43 studies involving 5,507 stroke patients and reported an odds ratio of 0.99 (95% confidence interval) for the association of stroke location and depression risk. This lack of association is hardly surprising given the heterogeneity in the way in which depression was assessed in these studies, the diverse timing of the assessments, the different definitions of lesion location (e.g., left frontal cortical versus left anterior), and the different neuroimaging methods used to determine lesion location. In spite of conflicting results, there are studies that have continued to report the association of PSD with left frontal hemisphere lesions and with proximity to the frontal pole.

e. Functional and cognitive impairment. The severity of poststroke impairment in activities of daily living is the factor most consistently associated with PSD. The severity of disability was found to be significantly related to PSD in 16 out of 18 studies reviewed by Hackett and Pickles[4]. The relationship between PSD and cognitive impairment (especially executive dysfunction) has been well established. Initial studies have demonstrated that stroke patients with major depression had significantly lower Mini-Mental State Examination scores than nondepressed patients with similar background characteristics who were matched for both lesion location and lesion volume. This finding was replicated in an independent study of stroke patients with left hemisphere lesions who were assessed during the first year after stroke.

f. Social support. The available evidence concerning PSD and social support is conflicting, probably because of significant heterogeneity in the definition and evaluation of social support. However, a prospective study found that lack of social support at admission was associated with the onset of PSD at 3-months follow-up[5].

Impact of depression on disease course

Numerous studies have examined the relationship between depression at the initial examination (which may range from a few weeks following stroke to 6 or more months following stroke) and functional and motor recovery. Five of six studies that examined whether severity of depression after acute stroke predicted severity of impairment in activities of daily living at 1 year or more of follow-up found that depression severity was an independent predictor of severity of impairment in activities of daily living.

Consistent with the previous findings, patients with PSD who responded to treatment with nortriptyline or fluoxetine showed significantly better improvement in activities of daily living than patients with PSD who did not respond to active treatment or placebo[6]. Similarly, a longitudinal study has shown that response to treatment of PSD with nortriptyline or fluoxetine over 12 weeks leads to improved cognitive function to the level seen in nondepressed stroke patients that lasts for more than 2 years.

Increased mortality associated with PSD is perhaps the most dramatic clinical phenomenon following PSD. Patients who developed PSD during the acute poststroke period had significantly higher mortality rates than similarly impaired stroke patients with no in-hospital depression (odds ratio53.4, 95% CI 51.4–8.4, p50.007).

Diagnosis of Post-stroke depression

Although PSD can occur shortly after a cerebrovascular event, it usually develops within the first few months following a stroke. The term ‘early-onset PSD’ has been proposed to refer to PSD occurring within the first 3 months after stroke, while ‘late-onset PSD’ refers to PSD developing after 3 months. In early-onset PSD, somatic depressive symptoms tend to be more numerous than psychological symptoms.

Diagnosis of PSD is complex due to the frequent presence of other symptoms, especially those associated with cognitive impairment, such as aphasia, agnosia, apraxia, and changes in memory. Additionally, some symptoms of stroke or of depression may overlap and be indistinguishable from each other. Symptoms common to both entities include sleep disorders, difficulty concentrating, and loss of appetite[1].

Although depressive symptoms are usually similar, some differences have been found between PSD patients and patients with depression but not associated neurological disease. PSD patients, especially those with right-hemisphere damage, are less likely to present dysphoric depression and more likely to present vegetative signs. Greater social withdrawal and fewer agitation symptoms have been reported in elderly stroke patients with depression compared to depressive patients with other conditions[1].

Treatment of Post-stroke depression

In the last 15 years, several reports have been published on the effectiveness of antidepressant therapies. In Cochrane revision published in 2008, pharmacotherapy (but not psychotherapy) showed to have a small but significant positive effect both in terms of a complete remission of depression and in reduction of depressive symptoms, but also with an increase in adverse events, and with relevant methodology issues across the studies. In another Cochrane revision on antidepressants in physically ill people, published in 2010, Rayner et al. found that ADs were effective, with greatest effect size at 6-8 weeks, but with more drop-outs at that time [7]. A more recent meta-analysis on 11 trials with 740 cases, evaluating overall pooled effect size, confirmed a significant advantage of ADs versus placebo in treatment of PSD (standardized mean differences [SMD] = -0.96; 95% CI = -1.41 to -0.51; P <0.0001). Antidepressant activity was more effective in older females with less severe depression[7].

a. TCAs: TCAs should be used with caution in elderly stroke patients due to possible occurrence of orthostatic hypotension, cardiac arrhythmia or in presence of glaucoma or prostate hyperplasia. Moreover, amitriptyline, nortriptyline and clomipramine have an anticholinergic activity, scoring 3 at Anticholinergic Burden Scale, the maximum score for risk of occurrence of delirium. Therefore, TCAs are not recommended as first-line choice for treatment of PSD.

b. SSRIs: the debate in recent years has focused more on safety than on the effectiveness of SSRIs. In fact, SSRIs use may cause some relatively frequent side effects, such as gastrointestinal symptoms, headache, sexual dysfunction and insomnia. There is a possible increased risk of bleeding complications, including intracerebral bleeding , probably as a result of inhibition of platelet aggregation. However, while a recent meta-analysis confirmed this risk, it also defined it to be very low[7].

c. SNRIs: patients treated with duloxetine or venlafaxine, as compared with those treated with sertraline and citalopram, showed not only a greater and faster improvement in depressive symptoms but also a better response on anxiety symptoms. In another open trial, the prophylactic use of duloxetine not only decreased the incidence of PSD, but also promoted rehabilitation, cognitive function and quality of life[7].

d. Other ADs: Mirtazapine has been showed to be efficacious in preventing and treating PSD, but may produce sedation and weight gain.

   Bupropion might be useful for its activating action, because of a possible double mechanism of action (inhibition of reuptake of both dopamine and norepinephrine), but data on its action on PSD are still lacking.

   Vilazodone showed to be an effective drug for treating MDD in adults, showed no cardiovascular risk and has a favourable weight-gain profile and therefore might be

useful for the treatment of PSD. However, no reports describe vilazodone effects on PSD.

Vortioxetine is an antidepressant with multimodal activity (serotonin 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist and a 5-HT transporter (SERT) inhibitor). Vortioxetine might become an important option for patients with PSD, because appears to have cognitive enhancing properties and efficacy in elderly patients. In fact, a recent meta-analysis on three DB-RCT, found that vortioxetine significantly improved cognition, independently by depressive symptoms. In particular, treatment with vortioxetine produced improvements in measures of executive function, attention/speed of processing, and memory. Lastly, coadministration of vortioxetine, even if in healthy volunteers, had no effect neither on aspirin or warfarin pharmacokinetics or pharmacodynamics, nor on arterial blood pressure and cardiac parameters including QTc, important issues in cerebrovascular patients. For these reasons, vortioxetine may be an important option for treatment PSD.

Prevention of Post-stroke depression

Perhaps the major advance in the treatment of PSD has been the demonstration of preventive treatment. The first statistically significant randomized controlled trial of prevention of PSD was conducted by Robinson et al.[8], published in 2008, in which 58 nondepressed acute stroke patients treated with escitalopram (5 mg/day for patients over age 65; 10 mg/day for patients ages 65 and under) over 1 year had an incidence of PSD of 8.5% compared with 11.9% for 59 patients receiving problem solving therapy and 22.4% for 59 patients receiving placebo. Controlling for age, gender, severity of stroke, and severity of impairment, the risk of onset of depression for placebo patients was more than four times greater than the risk for patients treated with escitalopram (adjusted hazard ratio54.5; 95% CI52.4–8.2, p,0.001).

However, according to latest Cochrane database, SSRIs reduced the average depression score (SMD 0.11 lower, 0.19 lower to 0.04 lower; 2 trials, 2861 participants; moderate-quality evidence), but there was a higher observed number of gastrointestinal side effects among participants treated with SSRIs compared to placebo (RR 2.19, 95% CI 1.00 to 4.76; P = 0.05; 2 studies, 148 participants; moderate-quality evidence), with no evidence of heterogeneity (I^2 = 0%). Accordingly, authors found no reliable evidence that SSRIs should be used routinely to promote recovery after stroke. Meta-analysis of the trials at low risk of bias indicate that SSRIs do not improve recovery from stroke. We identified potential improvements in disability only in the analyses which included trials at high risk of bias. A further meta-analysis of large ongoing trials will be required to determine the generalisability of these findings[9].

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