Determinants and consequences of post-stroke depression

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Post-stroke depression (PSD) is a very frequent and important consequence of stroke, but, in spite of the high number of papers aiming to clarify various aspects of this disorder, controversies about its incidence, its (biological or psychological) determinants, its consequences and its treatment still persist. In the present survey we have taken separately into account each of these issues, starting from a critical discussion of the main factors which can affect the estimates of the incidence of PSD. We have then surveyed and updated the debate between proponents of a neuroanatomical and a psychological interpretation of PSD. Our conclusions have been that the most recent evidence does not support Robinson's influential neuroanatomical model, assuming that a left frontal stroke could provoke a major PSD, indistinguishable from the functional forms of major depression. In the section devoted to the consequences of PSD, we have particularly taken into account the problem of the deleterious influence that PSD could have on functional recovery. The available evidence does not allow us to conclude if an improvement of PSD also leads to an improvement of the patient's functional status. As for the therapy of PSD, a pharmacological treatment with selective serotonin reuptake inhibitors has proven effective and safe, whereas psychological methods of treatment of patients and their families have not yet given conclusive results. Curr Opin Neurol 15:85–89.

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Current Opinion in Neurology 2002, 15:85–89

Abbreviation

PSD post-stroke depression

1350-7540

Introduction

Post-stroke depression (PSD) has been considered as the most frequent and important neuropsychiatric consequence of stroke, since at least one-third of stroke survivors experience depression both early and late after stroke [see review in 1] and since this condition can have an adverse impact on cognitive function [2], functional recovery [3] and survival [4].

The results of studies on the frequency, determinants and consequences of PSD have been, however, remarkably variable and controversial. Estimates of incidence of PSD range widely from 18 to 61% [5], as a function of methodological differences, such as the point at which patients are assessed relative to stroke onset and what instruments and criteria are used in assessment.

The determinants of PSD have been strongly debated between proponents of a neuroanatomical theory, assuming that PSD is usually caused by a lesion encroaching upon the left frontal areas [see discussion in 1] and supporters of a psychological theory, maintaining that PSD is a result of the psychosocial adjustment required by the disease [see discussion in 6]. Equally controversial are the consequences of PSD on cognitive function and functional recovery, since some authors have found, but others have not, a correlation between PSD and cognitive impairment and since the impact of PSD on rehabilitation and functional recovery is still under debate [7].

The aim of the present review is, therefore, to take separately into account some recent data relevant to the issues : of the incidence of PSD and of its determinants, taking as a reference point the influential neuroanatomical model of PSD proposed some years ago by Robinson and coworkers and reviewed by Starkstein and Manes [1], and of its consequences on cognitive functions, functional recovery and mortality. A final section of this review will be devoted to a short survey of data relevant to pharmacological and psychological treatment of PSD.

Factors affecting the estimates of incidence of PSD

Previous epidemiological studies [5] had shown that two methodological variables, namely the source of patients (stroke centres, rehabilitation units, community) and the time elapsed between stroke and assessment of depression have an important influence on the estimates of incidence of PSD, other important sources of variance

being the inclusion and exclusion criteria and the methods used for the diagnosis of depression. The importance of these last variables has been stressed by the contrasting results of two recent studies, based on large unselected cohorts of stroke survivors, which have obtained different estimates of the incidence of PSD, in spite of having gathered data from a similar source of patients (a stroke centre) and of having assessed depression at the same time interval (3 months) from stroke. The frequency of PSD was very low (11%) in the first study [8] and consistently higher (22–27%) in the second investigation [9], the lower incidence of the first study being probably due to three main reasons: (1) the exclusion of patients with previous histories of depression; (2) the inclusion of patients with vertebrobasilar strokes; and (3) a conservative approach to the diagnosis of depression, resulting from the use of lay interviewers. The importance of a previous history of depression as a risk factor for PSD had already been noted by other authors and has been recently confirmed by the contrasting results obtained by Dennis *et al.* [10] and by Kim and Choi-Kwon [11•] on large samples of stroke outpatients. In the first study, which had not considered a previous depression among the exclusion criteria, the frequency of PSD exceeded the 30%, whereas in the second study, which had excluded patients with a history of depression, the incidence of PSD just reached the 18%. This last study, having made a very detailed analysis of the lesion location, could also confirm that patients with vertebro-basilar strokes (i.e. with brainstem or cerebellar lesions) usually have a particularly low level of PSD.

Neuroanatomical and psychological determinants of PSD

The debate between proponents of a biological and of a psychological interpretation of PSD has been focused in recent years on the neuroanatomical model of PSD proposed at the beginning of the 1980s by Robinson's team [see 1 and 12 for reviews]. This model proposed that two qualitatively different (namely 'major' and 'minor') forms of depression may be ascertained within PSD. The 'major' form would be biologically determined, like the functional depression defined as 'major' by the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association [13] and would, therefore, be indistinguishable from the latter from a symptomatological point of view. This form of depression should not be interpreted as a psychological reaction to the dramatic consequences of stroke, because the correlation between severity of depression and degree of disability is sometimes only weakly positive. It has, on the contrary, very characteristic neuroanatomical correlates, being usually determined by lesions that grip onto the anterior parts of the left hemisphere (frontal cortex and underlying basal ganglia) and that, interrupting the monoaminergic pathways which connect the brain stem to the cortex, could provoke a monoamine deficiency in the brain. The 'minor' form of PSD, on the other hand, being symptomatically less well defined, and lacking precise neuroanatomical correlates, should be considered as a reaction to the disability induced by the cerebral lesion.

Unfortunately, several investigations, conducted in recent years to explore different facets of this complex model, have failed to confirm its validity. In particular, the distinction between 'major' and 'minor' forms of PSD, besides being questionable from the methodological point of view [see 8 and 14 for discussion] has proven incorrect from both the symptomatological and the statistical viewpoint. To check the symptomatological equivalence between major PSD and major functional depression (and respectively between minor PSD and reactive depression) Gainotti *et al.* [14] have constructed a new scale (the Post-Stroke Depression Rating Scale) which tried to distinguish motivated (reactive) from unmotivated (biologically determined) symptoms and which had been constructed by having in mind problems and symptoms of depressed stroke patients. This scale was administered to three groups of stroke patients classified as 'non depressed', 'minor depression' and 'major depression' and to a group of patients with a functional form of 'major depression'. Contrary to the predictions based on Robinson's model, the symptomatological profiles of patients with major PSD were more similar to those of patients with minor PSD than to those of patients with a functional major depression. Furthermore, unmotivated aspects of depression were on the foreground only in patients with endogenous depression, whereas motivated (reactive) aspects prevailed in patients with both major and minor forms of PSD.

To check from the statistical viewpoint the proposed distinction between major and minor forms of PSD Desmond *et al.* [8] have studied the distribution of total scores obtained on the depression rating scale by their cohort of stroke patients. The unimodal, rather than bimodal, shape of their graph has confirmed that PSD is a matter of degree rather than of kind.

Equally inconsistent with Robinson's model are results of studies which have tried to check the relationships between PSD and anatomical locus of lesion. As a matter of fact, even if some studies [10,11] have found that PSD is more frequently associated with anterior than posterior cortical lesions, other recent studies conducted on large groups of unselected stroke patients [7–9] have failed to confirm the relation between PSD and left hemispheric (or left frontal) lesions. Furthermore, results of the Cardiovascular Health Study [15] sought to assess the

association between PSD and lesions of the basal ganglia (that, according to Robinson's model, should affect mood by disrupting monoaminergic pathways) have paradoxically shown that depression scores were associated with non-basal ganglia lesions. Finally, a systematic review of all reports on the association of PSD with lesion location [16••] offered no support for the hypothesis that the risk of depression after stroke is affected by left hemisphere (and in particular by left frontal) lesions.

To account for objections addressed to their model, Shimoda and Robinson [17] have recently proposed that the anatomical correlates of PSD change over time and that only in the first weeks after stroke, is depression associated with left frontal lesions. Even this restricted version of the model meets, however, some difficulties, since Gainotti *et al.* [18] have shown that the symptom profiles and the anatomical correlates of PSD are not different in the acute and in more chronic stages and since Carson *et al.* [16••] have demonstrated that the relative risk for association of depression with left-hemisphere lesions does not change with time since stroke.

We must also say that both factual and conceptual objections have been addressed to the claim that the weak relation reported by some authors between severity of depression and degree of disability is inconsistent with a psychological interpretation of PSD. From the factual point of view, some authors [8–10,15,19,20] have shown that the degree of functional impairment accounts for a large part of the variation in the assessment of PSD. In particular, in the Cardiovascular Health Study [15] cognitive and functional impairment emerged as the single most significant factor associated with PSD. From the theoretical point of view, it has been observed [21] that the relation between functional impairment and severity of PSD is not direct, but mediated by the meaning that the patient attributes to this impairment. This meaning can obviously differ according to the lifestyle and the system of values of the patient, so that the same defect (e.g. a mild language disorder) can be considered as irrelevant by a manual worker but extremely distressing by a lawyer. The observation of a mild relationship between degree of impairment and severity of depression [11] is therefore not necessarily inconsistent with a psychological interpretation of PSD. On the other hand, the importance of psychological factors is stressed by results of a recent epidemiological study [20] which has shown that a number of psychosocial variables, such as divorce, institutionalization or lack of social support, are associated with PSD, leading the authors to conclude that depression is not more frequent in post-stroke patients than in older adults with similar levels of functional impairment of other origin.

Cognitive and functional consequences of PSD

The relationship between severe depression and intellectual impairment, originally reported by Robinson *et al.* [see review in 2] has been confirmed by some studies [22] but not by others [8,9,19] and remains therefore controversial, in spite of the fact that in a controlled treatment trial [23•] cognitive impairment was improved by pharmacological treatment of PSD. Equally controversial is the influence of PSD on recovery of functions, since some authors [9,24•] have confirmed that PSD is an independent predictor of poor long-term functional outcome, but other authors [7] have not confirmed a negative impact of PSD on functional recovery. This unsatisfactory state of affairs could be due to the confounding effect of antidepressants, since it is possible that in patients classified as depressed at the baseline, the positive effects of antidepressants may have afterwards counterbalanced the deleterious influence of PSD. If this hypothesis is correct, non-depressed and depressed but treated stroke patients should have a better recovery than not-treated patients with PSD. Four studies relevant to this issue [25,26•–28•] have been recently published, but unfortunately results of these studies have not been consistent. In the first study, comparing nortriptyline and fluoxetine with placebo, Robinson *et al.* [25] showed that nortriptyline produces a higher response rate than fluoxetine or placebo both in the treatment of PSD and in short-term recovery after stroke. In the second investigation, Gainotti *et al.* [26•] compared results obtained before and after rehabilitation on impairment and disability scales by three groups of stroke patients classified as non-depressed, depressed but treated with fluoxetine and depressed but non-treated. As expected, depression improved more in treated than in non-treated depressed stroke patients. Furthermore, the recovery of non-depressed and of depressed but treated stroke patients was significantly better than that of the non-treated depressed stroke patients. In line with these data are results of the third study, in which Chemerinski *et al.* [27•] examined the recovery of activities of daily living in patients with and without remission of their PSD. Patients whose mood improved on follow-up had a greater recovery in activities of daily living functions than patients whose mood did not improve. In contrast with these findings are, however, results obtained by Wiart *et al.* [28•], who matched results obtained on depression and disability scores by two randomized groups of depressed stroke patients, receiving respectively fluoxetine and placebo. Depression improved more in the fluoxetine than in the placebo group, but functional recovery was similar in the two treatment groups. Additional studies of post-stroke outcome should therefore try to clarify if and when improvement of PSD also improves functional status. In any case, the influence of PSD on post-stroke outcome

has been confirmed by a recent study [29•], which has shown that the presence of PSD 1 month after stroke increases the risk of mortality 12 and 24 months later. It must finally be noted that cognitive and functional consequences of PSD have important implications not only for individual stroke patients, but also for the decision analyses made at the societal level on the basis of quantitative evaluations of the health-related quality of life. Bosworth *et al.* [30••] have, indeed, shown that depressed stroke survivors assign to their health state a value significantly lower than that of the non-depressed stroke patients. Post *et al.* [31•] have therefore argued that depression should be included in the description of a health state after major stroke.

Pharmacological and psychological treatment of PSD

Several authors [7–9] had already stressed the fact that, although the treatment of PSD is often effective, very few patients are treated for this disorder and there is a surprising dearth of research focused on the treatment of PSD. From the pharmacological point of view, some authors [7,22] have argued that selective serotonin reuptake inhibitors, being non-sedative and devoid of cardiotoxic or anticholinergic side effects, could be safely used in the treatment of PSD [see 32• for a systematic review of this subject]. Studies reported in the previous section [26•,28•] have, indeed, confirmed that the selective serotonin reuptake inhibitor fluoxetine is safe and effective in reducing depression of stroke patients, although, according to Robinson *et al.* [25], nortriptyline could be superior to fluoxetine in the treatment of PSD. As for the psychological management of PSD, a recent paper by Kneebone and Dunmore [33] has tried to evaluate the research literature, reviewing this material against recommended standards for the empirical validation of treatment effectiveness. Although methodological limitations prevented any firm conclusion, cognitive behaviour therapy was identified as promising and worthy of further investigation. Support for a further evaluation of cognitive behaviour therapy in the treatment of PSD was also found in the evidence that one of its components (problem solving) contributes to a better functioning of the family of stroke patients. This last problem, namely the way of lessening the psychosocial difficulties of stroke patients and of their families has been studied recently in a randomized controlled trial, aiming to assess the impact of family support on stroke patients and their carers [34•]. This study has shown that family support significantly increased social activities and improved the quality of life of carers, although, except for possibly less depression, benefits to patients were not obtained.

Conclusion

Recent developments in the study of PSD have produced consistent answers to some debated questions, but have been unable to solve other relevant issues. Among the problems that have received a clarification, the most important probably concerns the determinants of PSD, whereas among the unresolved issues the most relevant refers to the influence of PSD on functional recovery. As for the first point, recent studies [7–9] and a systematic review of the literature [16••] have consistently shown that the left frontal lesions do not play a critical role in the pathophysiology of PSD. As for the second point, it remains unclear if pharmacological treatment of PSD, improving depression, also improves functional recovery [25,26•,27•], or if an effective treatment of depression can have no influence on the patient's functional status [28•]. Given the relevance of the problem, additional studies of this issue are urgently requested.

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