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ORIGINAL COMMUNICATION

The Italian multicenter observational study on post-stroke depression (DESTRO)

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Abstract Despite growing information, questions still surround various aspects of post-stroke depression (PSD). The Italian multicenter observational study Destro was designed to help clarify in a large sample the frequency and clinical impact of PSD. A total of 53 centers consecutively admitted 1064 patients with ischemic or hemorrhagic stroke, assessing them periodically in the first 9 months after the event. Patients with depression were followed for two years. Depression was diagnosed on clinical examination, verbal (Beck Depression Inventory) and non-verbal rating systems (Visual Analog Mood Scale), identifying the nosographic condition attributable to the mental state. The patient's clinical history, residual independence, and post-ictus quality of life were also taken into account.

PSD was detected in 383 patients (36 %), most of whom had minor depression (80.17 %), with dysthymia, rather than major depression and adaptation disorder. About 80 % developed depression within three months of the stroke. Cases with later onset tended to have less severe symptoms.

Risk factors were a history of depression, severe disability, previous stroke and female sex, but not the type and site of the vascular lesion. PSD was not correlated with any increase in mortality or cerebrovascular recurrences, but these patients had lower autonomy and quality of life ratings.

In conclusion, patients should be close observed in the first few weeks after a stroke in order to check for depression, which is more likely in those with clear risk factors and may spoil their quality of life.

Key words depression · stroke · risk factors · incidence

Introduction

Although several studies on the frequency and characteristics of post-stroke depression (PSD) have been done in the past few years, it is, however, difficult, to interpret existing data and to compare different studies because of methodological differences (e. g. diagnostic criteria, type of rating scales used, timing of evaluation and wide range of patient selection). Despite these problems, it is current opinion that at least 30 % of stroke survivors experience depression, both early and late after stroke [1–4], though the range is very wide (20–60 %). In particular, the numerous studies differ widely in their diag-

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nostic criteria, assessment methods (e. g. using dedicated scales or general tools), and criteria for admission (e. g. patients with or without aphasia, recent acute lesions or old chronic ones, admitted to rehabilitation units or sent home, etc.) [5–7]. Therefore, findings tend to depend heavily on the case list selected and the populations studied, often have little relation to the real epidemiological situation of PSD. In fact, most of the published studies are cross sectional, showing the frequency of PSD at different time-points after stroke and only a few studies have evaluated cumulative incidence during a prolonged period [8, 9].

In an attempt to answer some of these questions the DESTRO ("Depression in Stroke patients") multicenter observational study was designed, with a large case list of patients observed consecutively in an acute setting or during rehabilitation. The study set out to assess the frequency of PSD serially in the first few months after the stroke, defining its symptomatological features, time course and impact on residual disability. The first data from this study showed that female sex, degree of disability, previous cerebrovascular or depressive episodes were significantly associated with an increased risk of PSD. Combinations of these factors raised the risk of PSD exponentially, from 24.34 % to 89.09 % [10].

Material and methods

This was a multicenter, epidemiological-observational study, conducted in 2000–2003 on all patients with ischemic or hemorrhagic stroke (first or subsequent event) confirmed by neuro-imaging (CT or MRI), consecutively admitted to one of the study centers between 29 June 2000 and 31 July 2001. It involved 53 Italian neurology units for acute patients (94 %) or neurological rehabilitation centers (6 %), evenly distributed throughout the country.

We focused closely on the enrolment criteria in order to avoid excessively strict selection of the case list, which could have led to the exclusion of categories in which the depression was clinically important. All patients consecutively recruited were therefore eligible, except for cases of transient ischemic attacks (TIA), subarachnoid hemorrhage (SAH), age under 18 years, refusal to give informed consent, difficulty in longitudinal follow-up, significant cognitive decline (on the basis both of neuropsychological evaluation and of MMSE evaluation, with a cutoff score ≤ 10) or very severe disability (Modified Rankin Scale – MRS – score 5) [11]; aphasic patients were excluded if they were not able to understand and employ the Visual Analog Mood Scale (VAMS) [12].

The study protocol, already published elsewhere, comprised a first stage, when cases were registered, a second stage of selection, and a third stage of follow-up [13]. The selection stage, between 2–6 and 34–38 weeks after the acute event, was dedicated to checking for symptoms of depression, and patients attended four visits (1^{st}, 1 month ±2 weeks; 2^{nd}, 3 months ±2 weeks; 3^{rd}, 6 months ±2 weeks; 4^{th}, 9 months ±2 weeks). Patients presenting with symptoms of depression at one of these visits were then seen again three times (5^{th}, 1 year ±2 weeks; 6^{th}, 1.5 years ±2 weeks; 7^{th}, 2 years ±2 weeks). A pre-coded questionnaire was used to collect each patient's history. For ischemic strokes we used the Bamford et al. classification [14], and hemorrhagic strokes were classified as supra- or subtentorial.

Patients were classified as depressed if during selection period (within the first 9 months) they had presented with clinically evident symptoms of depression, with a Beck Depression Inventory (BDI) score of 10 or more [15]. Aphasic patients were enrolled if they indicated the "sad face" on the VAMS [12]. Symptoms of depression were also classified according to the DSM-IV and criteria for dysthymia in neurological disorders, revised by the WHO study group [16, 17]. We chose this approach in order to increase diagnostic accuracy, as, using DSM classification alone, a misdiagnosis of mood disorders was possible [18]. The WHO criteria ruled out the two-year duration criterion for diagnosis and established that for a correct classification of this disorder the concomitance of three groups of symptoms (nuclear, vegetative and functional) was necessary [17]. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to quantify the depression and follow its time course [19].

We also employed the Barthel Index (BI) and the Modified Rankin Scale (MRS) to assess disability [11, 20], and the SF-36 health questionnaire for quality of life [21]. Investigators in the various centers attended training sessions to unify the clinical evaluations and the use of the tests.

Statistical analysis

The clinical-demographic features of patients with and without PSD were compared by parametric and non-parametric tests. The association between the development of depression and the hypothetical risk factors, coded dichotomously, was first examined by univariate analysis, including a) sex, b) presence of aphasia, c) first event or recurrence, d) hemisphere involved and presence of hemispheric infarct, using the Bamford classification [14], e) previous depression, f) severe disability (MRS > 3) [11]. We then did a backward stepwise multiple logistic regression analysis to calculate the impact of each factor, corrected for the other variables, using the variables found to be significant in univariate analysis.

We assessed the impact of PSD on disability and quality of life by comparing the data for the depressed and non-depressed populations, using Cohen's effect size (ES) [22]. This measures the magnitude of a treatment effect or compares the mean of the experimental group with the mean of the control group. ES is defined as "small", with d value > 0.2 to 0.5, "medium", with $d > 0.5$ to 0.8, and "large", with $d > 0.8$.

Results

During the recruitment period we examined 1,817 patients, and 1,074 (59.1 %) were admitted to the study. Therefore, 743 subjects were excluded for the following reasons: 546 because informed consent was not obtained; 178 had a diagnosis of TIA; 9 had subarachnoid hemorrhage; 2 were younger than 18; 270 were uncooperative because of severe aphasia or cognitive deficit; 151 had an MRS score of 5. Lastly, 10 of the 1,074 patients admitted (0.93 %) failed to continue the study beyond the screening visit. The final total of 1,064 patients had the following main characteristics: mean age (yrs) 67.20 ± 11.76, range 18–92; 59.87 % were men and

40.13 % women. The majority (951, 89.38 %) had ischemic stroke, and only 113 (10.62 %) had parenchymal cerebral hemorrhage. This was the first acute focal cerebrovascular episode in 912 cases (85.71 %), and a recurrence in 152 (14.29 %). One hundred patients (9.40 %) had evident dysphasia.

At the end of the selection period 383 patients (36 % of the total) had developed depression (Table 1). Nearly 80 % of the patients (821, 77.16 %) were seen regularly for two years after the stroke. Drop-outs were due to organizational problems in 65 % of cases (patients who could no longer be reached, who withdrew their consent, or were lost to follow-up) and to intercurrent medical events in 35 %.

Table 1 summarizes the clinical and personal details of patients with depression and those without. The PSD group had a significantly higher frequency of women, patients with aphasia, previous stroke or depression, and major disability than the non-depressed group. There were no real differences in pathogenesis, type and site of the anatomical lesion.

Fig. 1 sets out the frequency of PSD at the various visits, and the cumulative prevalence of mood disorders at each visit. Depression appeared early, since it was detectable in 22.18 % of patients at the very first follow-up visit; the prevalence tended to rise at visits 2 and 3, then remained more or less stable between visits 3 and 4.

Of the 383 patients with PSD, 307 (80.16 %) developed the depression early (236 at visit 1, 61.62 %; 71 at visit 2, 18.54 %). Only in 51 cases (13.32 %) was it diagnosed between the fourth and sixth month (visit 3: 6 months ±2 weeks) and in 25 cases (6.53 %) at visit 4 (9 months ±2 weeks).

As regards the type of depression, in 80.68 % (309 cases) the diagnosis was dysthymia; in 2.87 % (11 cases) it was major depression, and in 8.36 % (32 cases) adaptation disorder. In the remaining 31 cases classification was either uncertain or not established. Nine of the 11 patients with major depression had a left hemispheric lesion (0.049, $\chi^2 = 6.05$).

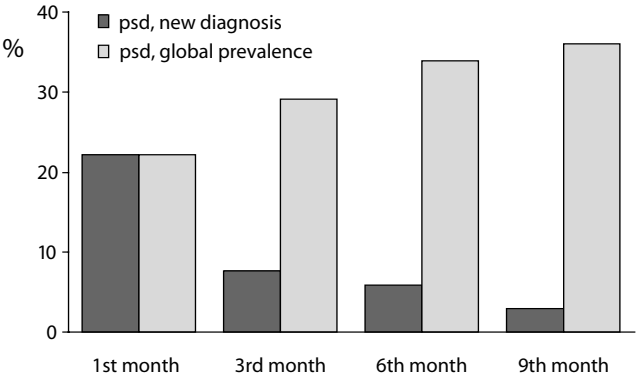

Fig. 1 New cases of PSD and overall prevalence (%) during follow-up

As shown in Fig. 2, the depressive symptoms, assessed using the MADRS, were more severe in patients with earlier onset, with no appreciable difference between those diagnosed between the first and sixth month (first three visits); they were less severe in cases who developed depression later (4^{th} visit) ($p < 0.05$, Dunnett's t-test vs. diagnosis at visit 1).

Analysis of the single components of the depressive disorder confirmed that groups with later onset had less severe symptoms than those diagnosed at visit 1, including the subclusters regarding somatic, cognitive and behavioral symptoms ($p < 0.05$, Dunnett's t-test vs. diagnosis at visit 1) and the relative homogeneity of the early-onset cases.

Table 1 Baseline characteristics of the two groups (No PSD and PSD)

Post-stroke depression (PSD)	No	Yes	p value
No. pts	681	383	N. A.
Age (years)	67.12 ± 11.56	67.35 ± 12.13	N. S., F = 1.10
Retired	67.60 %	64.29 %	N. S., $\chi^2 = 8.59$
Schooling > 8 years	21.71 %	22.35 %	N. S., $\chi^2 = 9.13$
Female sex	35.39 %	48.56 %	< 0.001, $\chi^2 = 17.71$
Ischemic lesions	89.28 %	89.56 %	N. S., $\chi^2 = 0.02$
Left hemispheric lesions	50.30 %	54.86 %	N. S., $\chi^2 = 1.97$
Cortical lesions in carotid territory (TACI-PACI)	45.54 %	52.06 %	N. S., $\chi^2 = 3.70$
Aphasic	7.20 %	13.32 %	0.001, $\chi^2 = 10.78$
First event	88.55 %	80.68 %	< 0.001, $\chi^2 = 12.39$
Previous depression	4.41 %	15.67 %	< 0.001, $\chi^2 = 40.14$
Severe disability (MRS score > 3)	16.89 %	37.86 %	0.001, $\chi^2 = 58.39$

N. A. Not Applicable; *N. S.* Not Significant; *MRS* Modified Rankin Scale; *TACI* Total Anterior Circulation Infarcts; *PACI* Partial Anterior Circulation Infarcts

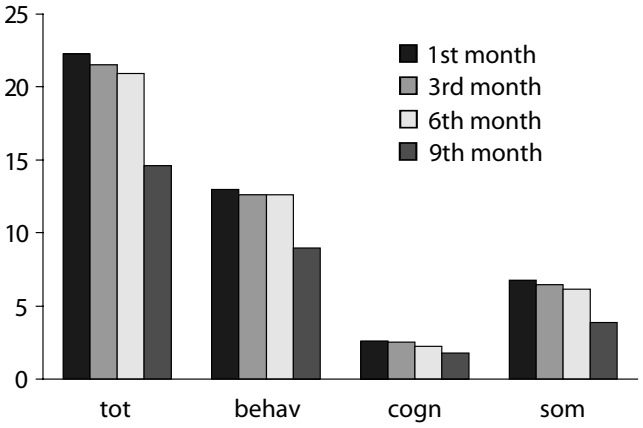

Fig. 2 Baseline severity of depressive symptoms showing Montgomery-Asberg Depression Rating Scale (MADRS) score subclusters, in relation to time of onset of PSD (*tot* total; *behav* behavioral; *cogn* cognitive; *som* somatic)

Fig. 3 shows that the first three groups (diagnosis at visits 1–3) had close and significantly improved MADRS scores at follow-up ($p < 0.001$). The group with later onset showed no significant differences. The significant difference between the MADRS scores for groups 1 and 4 was confirmed at follow-up ($p < 0.05$, Dunnett's t-test).

During follow-up, there were 104 drop-outs in the PSD group (27.15 %) and 139 (20.41 %) in the group without PSD ($\chi^2 = 6.325$, df = 1, $p = 0.01$). However, about 60 % [62] of the 104 PSD drop-outs were due to organizational reasons (28 withdrew consent, 34 could no longer be reached). There was no significant difference in the numbers of intercurrent medical events causing patients to drop out (38 in patients with PSD and 47 in those without), including myocardial infarction (respectively 0.26 % and 1.47 %), recurrent stroke (3.13 % and 3.08 %), and deaths (5.48 % and 4.85 %). On the whole, however, patients with PSD had a higher mean number of more intercurrent medical events than the non-depressed patients (1.92 vs. 1.54, $p < 0.001$, $t = -3.36$).

The frequency of antidepressant treatments rose gradually, from 19.35 % at visit 1, to 35.16 % at visit 2, 49.27 % at visit 5, 46.98 % at visit 6 and 44.32 % at visit 7.

PSD patients had significantly more severe initial functional impairment than non-depressed patients, as indicated by the BI values (Table 2). The ES was moderate/severe (range 0.53–0.82). During follow-up, PSD patients still had significantly more severe functional impairment than non-depressed patients, with a moderate ES (range 0.53–0.75). Patients without PSD and those with early-onset PSD (diagnosis at visit 1) showed significant improvement from baseline BI during follow-up ($t = -1.04$ and $t = 9.08$ respectively, both $p < 0.001$). In this table, the comparison were performed between patients who or never developed PSD during selection period. Therefore, patients who at baseline and/or in the first visits were not depressed and became depressed during the selection period were not included in the comparison.

The impact on the quality of life, assessed using the SF36, showed that PSD had considerably more impact than the stroke alone. Assessed serially (Fig. 4) in patients with early-onset PSD, there were significant differences in each domain, with a moderate/severe ES (from –0.55 for physical health at visit 1 to –1.40 for mental health at the last visit). At the last visit, 11.3 % of PSD patients were living on their own, somewhat fewer

Table 2 Barthel Index (BI) values at baseline in patients with PSD vs never depressed, and time of onset

Diagnosis	No. pts with PSD	Mean BI	No. pts without PSD	Mean BI	Effect size
Visit 1	235	67.45	680	84.56	–0.72
Visit 2	71	83.17	592	92.65	–0.59
Visit 3	51	83.53	552	94.32	–0.82
Visit 4	25	88.80	553	95.14	–0.53

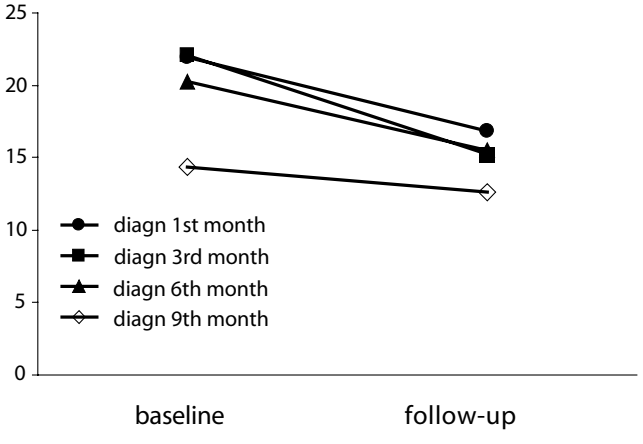

Fig. 3 Montgomery-Asberg Depression Rating Scale (MADRS) score at baseline and at the last follow-up visit in relation to time of onset of PSD

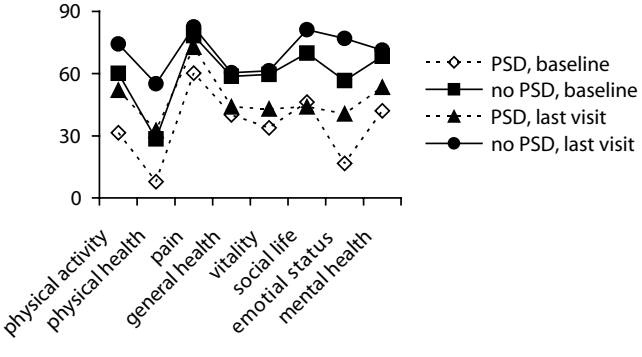

Fig. 4 SF-36 score at baseline and at the last follow-up visit in patients diagnosed as having PSD at visit 1, and non-depressed patients

than the 17.8% of those without PSD ($\chi^2 = 6.06$, $p < 0.05$).

Discussion

Extensive studies are needed, using simple, repeatable methods, with adequate follow-up, in order to answer several questions related to PSD [6, 23]. The DESTRO study meets most of the requirements set out in reviews [2, 23], in that the enrolment criteria admitted patients with aphasia, as long as they had no major comprehension difficulties, so as to obtain a sample representing the post-stroke population as fully as possible. The inclusion or exclusion of aphasic patients is considered to be one of the main factors causing the lack of homogeneity between data on whether or not there is a correlation between PSD and anatomical site of the lesion [23]. However, despite the efforts, it must be remembered that our study was unable to evaluate mood changes in all patients examined, and therefore it is representative of most of stroke survivors, but not all. In fact, besides extremely disabled patients (see exclusion criteria), a large number of aphasic patients with severe comprehension deficit were not enrolled because of incapacity to understand and employ VAMS. In future studies, the use of recently published specific scale for aphasics as ADRS (Aphasic Depression Rating Scale) should reduce this selection bias [24]. A possible other selection bias might be due to the use of BDI, a self-administrating rating scale, previously used in other studies on PSD [25, 26], but designed for functional depression. Recently, Aben and coworkers underscored the validity of BDI as screening instrument for PSD [27]. However, the choice of cut off scores of used scales (BDI and VAMS) for diagnosis of depression was due to the need for the protocol in a multicenter study to be simple and reliable. This may have penalized some specific diagnostic features, but such an ample study involving so many centers could not impose complex evaluation systems.

In the last few years an interesting debate has arisen on how to classify clinical pictures involving depressive symptoms. There are questions regarding, in particular, the temporal criterion employed in the DSM-IV for the diagnosis of dysthymia (two years) and for adaptation disorder with depressed mood, evolving favorably within six months. The DESTRO study used the specific checklist issued by the WHO to increase diagnostic accuracy and to reduce the risk of misdiagnosis of mood disorders. The WHO criteria ruled out the two-year duration criterion for diagnosis, and established that for a correct classification of this disorder the concomitance of three groups of symptoms (nuclear, vegetative and functional) was necessary [17]. As reported in the *Method* section, this approach, focused on mood disorders in neurological disorders, may improve diagnostic criteria respecting to diagnostic criteria, as DSM ones, validated in psychiatric patients without neurological impairment. According to this diagnostic approach, most cases were classified as dysthymic disorder [17]. Therefore, the prevalence rate of major depression, very much lower (2.87%) than that of the recent meta-analysis of Robinson (19.3%) [4], is probably due both to these new diagnostic criteria and to difference in casuistry.

The feasibility of the study, in terms of the proportion of patients lost to follow-up, is comparable with other recent reports on sizeable case lists [28].

The results in the large population admitted to the DESTRO study confirm the clinical impact of PSD and indicate the times of onset, risk factors, and the consequences of the depression. In particular, our data were consistent with those of previous studies regarding the overall frequency of PSD [1, 2], and especially with those of other longitudinal studies on PSD [8, 9]. Similarly, our data were consistent with those of previous studies regarding the early occurrence of PSD, in particularity within three months of the stroke [8, 9].

As published elsewhere [10], our findings confirm the presumed multifactorial origin of PSD, showing a significant association between both constitutional (female sex) [29–31] and clinical-functional factors (previous stroke, previous depressive disorders, degree of residual disability) [29, 32–34] and occurrence of PSD. However, some potential risk factors were not evaluated, such as living alone, previous stroke or neuroticism [35, 36], because we were unable to record accurate anamnestic features in all patients, especially in the aphasics ones.

The clinical data seem to distinguish between early-onset and later-onset (after 6th month) cases. Patients developing PSD early, as indicated by Verdelho et al., presented more serious symptoms of depression, assessed using the MADRS, than those who developed the disorder later [28]. However, even if somatic and autonomic symptoms due to stroke (and not to PSD) might partly explain the higher MADRS scores observed in early depressed patients, it is important to note that all subclusters of MADRS (somatic, cognitive and behavioral) were similar among patients with early occurrence of PSD and different from those with late onset.

In agreement with previous publications [30, 31, 37, 38], we found no relation between the side and type of vascular lesion and the development of PSD. However, the investigation was not addressed to the study of the neuroanatomical correlations of PSD. A more detailed evaluation of correlations between clinical syndromes and PSD might be of practical usefulness. A wider use of MRI might be useful, for future studies on PSD, to clarify the neuroanatomical correlates. Recently, MRI-based studies showed an association between PSD and lesions

affecting the frontal-subcortical circuits, especially on the left side [39].

PSD did not involve any increase in major vascular events – at least in the short term. This appears to differ from other observations, based, however, on longer periods, of higher mortality among PSD patients [40, 41]. This may well reflect the fact that a good proportion of our case list were receiving antidepressants, which are reported to improve survival of stroke patients [42].

PSD patients had more serious functional impairment, both initially and during follow-up, confirming the relations with disability described in previous reports [43–45]. Great care is needed in assessing the variables that can influence functional recovery in depressed patients. In addition, as already reported [46, 47], PSD substantially affects quality of life, making it difficult for patients to cope on their own.

In conclusion, the findings of the DESTRO study highlight the speed of onset and clinical impact of PSD. This disorder arises in more than one third of cases and its clinical and functional repercussions are serious.

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