

Depressive-, Cognitive- or Stroke-Related Risk Factors of Post-Stroke Depression: Which One Could Better Help Clinicians and Patients?

Rebecca Perrain^{1,2}

David Calvet³⁻⁵

Vincent Guiraud³⁻⁵

Lila Mekaoui¹

Jean-Louis Mas³⁻⁵

Philip Gorwood^{1,2,5}

¹GHU Paris Psychiatrie et Neurosciences, CMME, Hôpital Sainte-Anne, Paris, France; ²University of Paris, Paris, France; ³GHU Paris Psychiatrie et Neurosciences, Department of Neurology, Hôpital Sainte-Anne, Paris, France; ⁴University of Paris, FHU Neurovasc, Paris, France; ⁵Institute of Psychiatry and Neuroscience of Paris, INSERM U1266, Paris, France

Purpose: Post-stroke depression (PSD) affects one third of stroke survivors, with multiple severe negative consequences. We aim to assess the weight of four different types of clinical risk factors for PSD.

Patients and Methods: We conducted a prospective cohort study in a stroke centre. After stroke, patients were assessed for cognitive performances, psychiatric standardized questionnaires and socio-demographic features. They were called three months after and assessed for major depressive episode using DSM criteria.

Results: PSD was diagnosed in 8 of the 59 (13.6%) patients enrolled in the study. After multivariate analysis, only “previous history of depressive episode” remained a significant predictive factor for PSD, the model explaining 19% of the total variance (OR=18.0; $p=0.002$). Patients with a previous history of depression had a 10-fold increased risk for PSD.

Conclusion: Previous history of depression is confirmed as a strong risk factor for PDS and allow the identification of an at-risk sub-group of patients.

Keywords: post-stroke depression, depression, stroke, risk factors, prevention, cohort

Introduction

Worldwide, strokes are the second leading cause of death, after cardiovascular diseases.¹ In France, strokes are the first leading cause of acquired disability in adults,² leading to more quality of life issues when compared to other vascular diseases, such as myocardial infarction.³ Post-stroke depression (PSD) is affecting one third of stroke survivors, with negative consequences such as higher mortality⁴ and poor recovery.⁵ The recent “Stroke early management guideline” from the American Heart Association and American Stroke Association, briefly mentioned PSD, with no specific recommendation regarding efficient screening tools, recommended ways to detect the diagnosis or appropriate treatment strategies.

Several reviews identified a set of PSD risk factors, stressing the role of mood-related factors such as previous history of mood disorder, pathological crying at stroke onset, or family history of depression.^{4,6-9} Socio-demographic factors and global medical factors were also analysed with some of them being identified as PSD predictors. However, results are still discordant.⁷⁻⁹

Cognitive status, at the interface between neurologic damages and psychiatric symptoms, was analysed as well. Post-stroke cognitive impairment has been already associated with PSD.^{4,10-12}

Correspondence: Rebecca Perrain
Clinique des Maladies Mentales et de l'Encéphale, Sainte-Anne Hospital, GHU Paris— Psychiatrie & Neurosciences, 100 rue de la Santé 75674 Paris Cedex 14, Paris, France
Tel +33 1 45 65 83 64
Fax +33 1 45 65 76 56
Email r.perrain@ghu-paris.fr

Cognitive impairment is also observed independently during major depressive episodes,¹³ and could be ongoing afterwards. Delayed memory,¹⁴ executive functions and attentional skills¹⁵ have been shown to be impaired even after reaching clinical remission.¹⁶

Executive and attentional dysfunctions are often coupled. Recent findings have shown that attentional dysfunction could be the *primum movens* of all depression-related cognitive impairment.¹⁷ Other studies suggested that psychomotor retardation could reflect the « burden » of past depression as being correlated with the number of previous depressive episodes.^{17,18}

To our knowledge, there is a lack of studies comparing these different risk factors, and among them neurocognitive impairments, assessing their weight in PSD outcome. Some results suggested that depressive-related symptoms were the most predictive item, but cognitive impairment was always assessed in a global way.⁸

We therefore assessed the weight of four different types of risk factors for PSD. We distinguished those related to psychiatric and mood-related morbidity, those depending on non-psychiatric co-morbidities and stroke-related features, the ones related to specific cognitive impairment – at the interface between neurologic damages and psychiatric symptoms – and lastly the generic ones such as socio-demographic features.

Patients and Methods

We conducted a prospective cohort study with consecutive inclusions in a stroke unit, at Sainte-Anne hospital, Paris.

Inclusion and Exclusion Criteria

- Inclusion criteria were (1) age over 18, (2) ischemic or haemorrhagic stroke within 14 days of stroke onset confirmed by magnetic resonance imaging or computed tomography scan.
- Exclusion criteria were (1) poor global medical condition precluding an hour participation in assessments, including hemiparesia (N=35, 10.9%), (2) an impossible follow-up, (3) not a fluent French speaker, (4) aphasia with a language National Institute of Health Stroke Score (NIHSS) item ≥ 2 or a Boston Diagnostic Aphasia Examination < 8 , (5) hemineglect according to the bells test, (6) antidepressant taken at the stroke onset (as studies showed a preventive effect and then a lower rate of PSD with preventive antidepressant treatment),¹⁹ (7) major depressive episode present at the stroke onset (8) adults under legal

protection and pregnancy or breastfeeding. (9) subdural haematoma, subarachnoid haemorrhage, thrombophlebitis and post-surgical stroke.

Estimated Sample Size

We used the 2.19 odds ratio published in our recent meta-analysis on risk factors associated with PSD regarding “previous history of depression” (the most informative marker),⁸ and a PSD prevalence of 17.7% for PSD according to another recent meta-analysis⁷ to compute estimated sample size. We estimated that 76 patients were needed to detect a significant role of such risk factors at the end of the cohort, with a risk of 5% and a power of 90%. As the tests demand different skills, we estimated on a preliminary test sample that one patient out of four would roughly be able to be finally tested, raising the number of patients to be included to 304.

Demographic Data

The following demographic data were assessed: age, gender, profession, school level, marital status.

Clinical Assessment

Data collection and clinical assessment occurred within 14 days of stroke onset, from patient bedside.

1. Stroke characteristics: were assessed including lesion side (right, left, bilateral, median) and stroke severity with the NIHSS.²⁰
2. Cognitive tasks: were performed directly from patient bedside, and included the d2 test (sustained and selective attention),²¹ the Dubois’s 5 words test (verbal memory),²² the clock drawing test (executive functions, spatial organisation),²³ and the digit span trial (working memory, verbal memory).²⁴ The test description is available in [Supplemental Materials](#).
3. Psychiatric assessment: included the screening of actual and past depressive episodes with a semi-structured interview (Mini International Neuropsychiatric Interview, MINI-depression, Fifth edition), depressive symptoms being assessed with the Beck Depression Inventory.²⁵ Patients were asked for other past psychiatric history (psychiatric care, treatments). Patients also filled-in the Clinical Global Impression and the Standardised Assessment of Personality Abbreviated Scale (SAPAS), a questionnaire of 8 questions to detect

personality disorder. Score ≥ 3 indicate a personality disorder.²⁶ Alcohol Use Disorders Identification Test (AUDIT-C) was completed: the threshold value is 5 for men and 4 for women.²⁷ Heavy Smoking Index was completed to detect tobacco use disorder (threshold value of 2).²⁸

Three months after the first visit, all patients were called by a psychiatrist and assessed for depression using DSM criteria with MINI-depression. The single assessment of depression after 3 months is based on a previous work, showing that 85% of PSD occurred in the three months following stroke.²⁹

This study was conducted in accordance with the Declaration of Helsinki and was approved by the French National Ethics Committee called “Comité de Protection des Personnes Sud-Méditerranée II” which reference number is 217 R15. The identification number of the protocol was 2017-A00339-44. All patients gave written informed consent prior to participation. All data were recorded anonymously. This study was registered on clinicaltrials.gov (NTC04008719).

Statistical Analyses

Student *t*-test was used to compare continuous variables and χ^2 test to compare categorical variables. Fisher's exact test was used when minimum expected count was not obtained. Initial data were analysed to study correlation between variables: Pearson correlation was used. When variables were not normally distributed, Spearman test was used. Logistic regression was performed to detect in a multivariate way which parameters were predictive of PSD. For all tests, the threshold of significance was set at $p \leq 0.05$.

Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the confirmed predictive factors were calculated. Positive predictive value (PPV) is the proportion of patients with positive predictors that will have PSD ($PPV = \text{True Positives} / [\text{True Positives} + \text{False Positive}]$), and the negative predictive value (NPV) is the proportion of patients with negative predictors that will not have PSD ($NPV = \text{True Negatives} / [\text{True Negatives} + \text{False Negatives}]$).

All statistical analyses were performed with IBM SPSS Statistics for windows, version 23.0. Armonk, NY:IBM Corp.

Results

Among 321 consecutive stroke patients screened between May 2017 and October 2017, 59 were finally included (Figure 1).

Comparison Between Included and Excluded Patients

There was no difference between the recruited population compared to the others regarding gender. However, the included patients were younger ($p < 0.001$) with a lower level of severity considering NIHSS ($p < 0.001$).

Sample Characteristics at Baseline

Fifty-three (89.8%) ischaemic strokes were detected, the other being haemorrhagic. Our sample included 21 (35.6%) women, mean age was 61.9 (SD18.5).

Clinical, imaging characteristics and cognitive tests (Table 1) were not independent, as the NIHSS, working memory, verbal memory and age were correlated with some parameters of the d2 Test, and the number of past depressive episode was correlated with the percentage of d2 mistakes.

Prevalence of PSD, Univariate and Multivariate Analyses

Three months later, two patients could not be assessed. One died (stroke recurrence) and one was lost to follow-up.

PSD was diagnosed in 8 patients (13.6% of total sample), all of them being men.

Univariate analysis (Table 2) identified four variables associated with PSD: previous history of depression, previous history of hypertension, tobacco use disorder and male gender, but none of the cognitive test results. We then analysed the associated variables in a logistic regression analysis (Table 3) apart from gender because of the absence of contrast (100% of PSD being males). Only “previous history of depressive episode” remained a significant predictive factor, the model explaining 19% of the total variance ($OR=18.0$; $p=0.002$). When considering only male patients, the model explained 33% of the total variance ($OR=42.0$; $p=0.001$).

Calculated PPV and NPV were, respectively, 46% and 95% for previous history of depression. When considering only male patients, we obtained PPV 75% and NPV 93%.

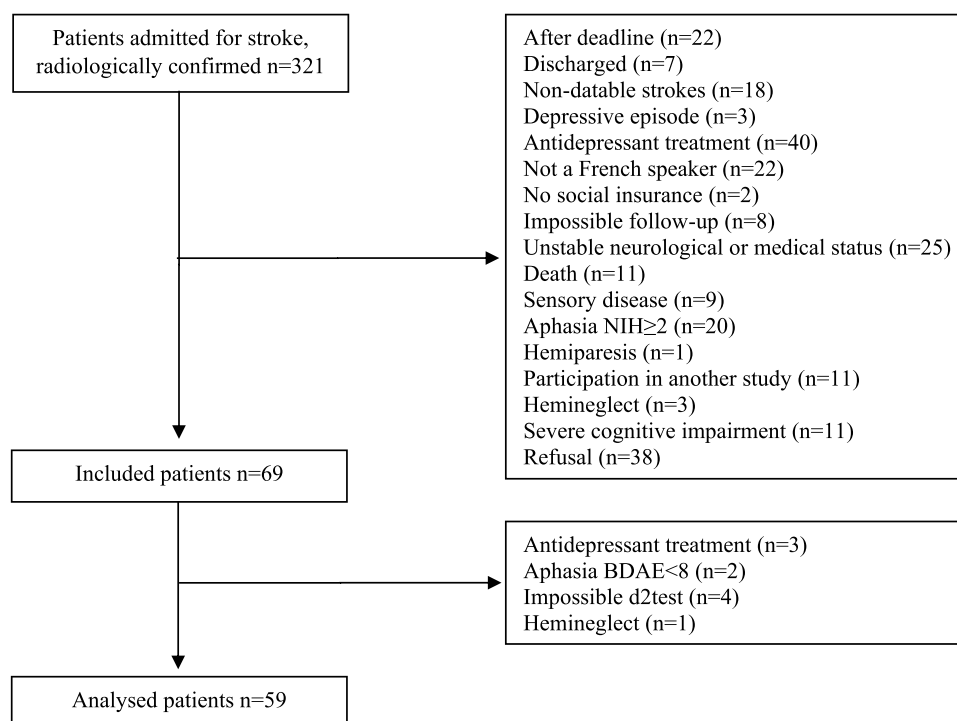


Figure 1 Flow-chart of the study.

Discussion

In a study analysing 59 consecutive patients hospitalized in a neurological department specialized in stroke, 14% developed a PSD three months later. A past history of depression assessed at inclusion was the only predictive factor of future PSD when using a multivariate approach, with a positive predictive value of 46% and a negative predictive value of 95%. Patients with a previous history of depression had indeed a 10-fold increased risk for PSD. Contrary to our initial hypothesis, no cognitive test performed at the acute period of the stroke was predictive of later PSD.

Patients included in our study were significantly younger and clinically less severe (considering NIHSS) than the rest of the sample. This is explainable as aphasia and hemiparesia were exclusion criteria and are distinct NIHSS items. We assume that it is a selection bias, limiting the generalisation of our results and narrowing its predictive value to patients that are questionable.

In our sample, depression prevalence three months after stroke is 14%, contrasting with the 30% described in previous studies,^{4,29} but close to a recent meta-analysis that found a pooled prevalence of PSD of 17.7%.⁷ Our strict DSM assessment avoided over-estimation, but our

method excluded aphasic and clinically instable patients, leading indeed to younger, more professionally active patients; therefore, to patients with a lower risk of developing PSD. Moreover, we chose a single assessment of PSD after 3 months whereas other studies frequently rely on a follow-up of 6 months.⁶

We aimed at identifying predictive factors for PSD and after logistic regression, only the item “previous history of depression” remained relevant. The fact that no cognitive test was associated with PSD, could be due to the small sample size leading to a lack of statistical power as an association between cognitive impairment and PSD has been already detected.⁴ On the other hand, these studies assessed cognitive functions in a global way that did not allow specific predictive features.^{30,31}

Previous history of depression is a simple feature and can be accurately assessed with brief semi-structured interview, such as the MINI. Our results stress the need of a systematic interview of patients with stroke, at the acute phase, to screen and detect unnoticed past depressive episodes. Previous history of depressive episode is a well-known risk factor for depressive recurrence.³² Genetic factors as polymorphisms of serotonin transporters confer vulnerability to depression and have been identified as risk

Table I Sample Characteristics of 59 Patients Hospitalized for a Stroke. There Was No Missing Value

Demographic Characteristics	n (%) or Mean \pm SD	Clinical Characteristics	n (%) or Mean \pm SD	Medical History Previous History of	n (%) or Mean \pm SD
Age	61.7 \pm 18.3	BDI	8.4 \pm 5.8	Depression	13 (22.0)
Women	21 (35.6)	Depressed duration (months)	2.4 \pm 6.5	Bipolar disorder	0 (0)
Profession (Yes)	29 (49.2)	SAPAS	17 (28.8)	Anxiety disorder	0 (0)
School level		Clock test	27.2 \pm 3.3	Schizophrenia	0 (0)
Primary	3 (5.1)	Verbal memory (Dubois's)	9.9 \pm 0.5	Substance use disorder	1 (1.7)
Secondary	17 (28.8)	Auditive memory (DSF)	8.7 \pm 1.7	Suicide attempt	1 (1.7)
High school degree	5 (8.5)	Working memory (DSB)	5.6 \pm 2.2	Stroke	7 (11.9)
Bachelor level (1st, 2nd, 3rd year)	9 (15.3)	NIHSS	2.3 \pm 5.3	Hypertension	27 (45.8)
Master level (1st, 2nd year)	16 (27.1)	Ischaemic stroke	53 (89.8)	Myocardial infarction	2 (3.4)
>Master level	9 (15.3)	Stroke side		Diabetes	9 (15.3)
Marital/living status		Right	25 (42.4)	Alzheimer	0 (0)
Single	9 (15.3)	Left	26 (44.1)	Parkinson	0 (0)
Couple	4 (6.8)	Bilateral	2 (3.4)		
Cohabitation	1 (1.7)	Median	6 (10.2)		
Married	30 (50.8)				
Divorced	8 (13.6)				
Widowed	7 (11.9)				

Abbreviations: SD, Standard Deviation; BDI, Beck Depression Inventory; SAPAS, Standardized Assessment of Personality – Abbreviated Scale; Dubois's, Dubois's 5 words; DSF, digit span forwards; DSB, digit span backwards; NIHSS, National Institute of Health Stroke Score.

factors for post-stroke depression.^{4,33} Stroke could be considered as a biopsychosocial stress leading to recurrence. Another hypothesis of possible mechanism of the impact of previous history of depressive episode on PSD, is that previous depressive episodes have consequences like a possible cognitive scar that could lead to recurrence.¹⁵

Some limits should be stressed in the present study. First, the recruitment was monocentric and hospital-based, limiting results generalizability. However, this approach allows a complete recruitment of all stroke patients comparing with other studies in rehabilitation units and a relatively low attrition rate was observed in our sample. Second, we excluded patients with severe

stroke, therefore all patients with significant aphasia, which creates a bias and explains the high drop-out between patients screening and inclusion. However, as language is needed to obtain patients' agreement and is required to understand the different cognitive tests, such bias is difficult to avoid. Anyhow, it means that the conclusions drawn from this study have to be limited to patients able to communicate and to perform cognitive tests. Third, the sample size remains relatively small and may have lowered statistical power. Finally, all depressed patients were men, which constitutes a sample bias and is strikingly not in line with previous reviews.

Table 2 Univariate Approach of Factors Describing a Sample of 59 Patients with Stroke, According to the Development (or Not) of a Post-Stroke Depression 3 Months Later

Factors	Post-Stroke Depression								Statistics			
	No				Yes							
	Mean	SD	n	%	Mean	SD	n	%	χ^2	t	df	p-value
Depressive-related												
Previous history of depression			7	14.3			6	75.0	14.40		1	<0.001
Depressive symptoms (BDI)	7.73	4.95			11.38	9.40				-1.07	7.65	0.32
Time duration of depression (months)	1.49	5.64			8.63	8.77				-2.23	7.97	0.06
Number of past episodes	0.12	0.33			0.88	0.99				-2.13	7.26	0.07
Tobacco consumption score	0.16	0.90			1.38	2.26				-1.50	7.36	0.18
Tobacco use disorder			1	2.0			2	25.0	7.30		1	0.007
Alcohol consumption score	2.51	2.11			5.38	4.10				-1.93	7.62	0.09
Alcohol use disorder			11	22.4			4	50.0	2.70		1	0.10
Personality disorder (SAPAS)			14	28.6			3	37.5	0.26		1	0.61
Previous history of suicide attempt			0	0.0			1	12.5	6.23		1	0.14
Non-psychiatric & stroke-related												
CGI	2.82	1.11			2.88	1.46				-0.13	55	0.90
Stroke type			1	12.5			5	10.2	0.04		1	0.84
Lesion side Right			20	40.82			3	37.5	4.89		3	0.18
Left			24	48.98			2	25.0				
Bilateral			1	2.04			1	12.5				
Median			4	8.16			2	25.0				
NIHSS	1.94	5.52			2.25	2.61				-0.16	55	0.88
Previous history of stroke			5	10.2			1	12.5	0.04		1	0.84
Previous history of hypertension			20	40.8			7	87.5	6.01		1	0.021
Previous history of diabetes			8	16.3			1	12.5	0.08		1	1.00
Previous history of myocardial infarction			1	2.0			1	12.5	2.22		1	0.14
Cognitive-related												
Spatial organisation (clock test)	27.00	3.37			29.25	1.39				-1.85	55	0.07
Verbal memory (Dubois's 5 words)	9.86	0.54			10.00	0.00				-0.74	55	0.46
Verbal memory (DSF)	8.76	1.58			9.13	1.96				-0.60	55	0.55
Working memory (DSB)	5.61	2.62			5.88	1.46				-0.32	55	0.75
Attention (d2 test)												
GZ (number of marked items)	482.63	762.68			414.13	63.14				0.25	55	0.80
F1 (number of omission mistakes)	16.20	15.82			24.50	18.94				-1.34	55	0.19
F2 (number of commission/confusion mistakes)	0.94	2.00			1.38	1.69				-0.58	55	0.56
F total (total number of mistakes)	17.14	16.09			25.88	18.94				-1.39	55	0.17
BR (number of correctly marked items)	145.96	48.18			148.63	12.28				-0.16	55	0.88
KL (BR-F2)	145.02	48.51			147.25	12.89				-0.13	55	0.90
Socio-demographic												
Gender (female)			19	38.8			0	0.0	4.65		1	0.042
Age	61.41	19.33			62.50	7.64				-0.28	25,3	0.78
Study level Primary/secondary school			18	36.7			1	12.5	4.76		4	0.33
High school degree			3	6.1			2	25.0				
Bachelor level (1st, 2nd, 3rd year)			7	14.3			2	25.0				
Master level (1st, 2nd year)			13	26.5			2	25.0				

(Continued)

Table 2 (Continued).

Factors	Post-Stroke Depression								Statistics			
	No				Yes						df	p-value
	Mean	SD	n	%	Mean	SD	n	%	χ^2	t		
>Master level			8	16.3			1	12.5			1	0.96
Profession (yes)			24	49.0			4	50.0	0.01		1	
Marital/living status (not alone)			28	57.1			6	75.0	0.91		1	0.45

Abbreviations: SD, standard deviation; df, degree of freedom; BDI, Beck Depression Inventory; SAPAS, Standardized Assessment of Personality – Abbreviated Scale; CGI, Clinical Global Impression; NIHSS, National Institute of Health Stroke Score; DSF, digit span forwards; DSB, digit span backwards; KL, concentration performance index.

Conclusion

We confirm the strength of mood-related risk factors for PSD and allow the identification of an at-risk sub-group of patients for whom a specific follow-up monitoring their mood is needed. Further placebo-controlled trials are

needed to recommend preventive antidepressant for this sub-group. Many studies are involved in identifying new complex biomarkers, but the fact that a simple clinical factor, such as past depressive episode, is driving the majority of predictive factor in the present study could

Table 3 Logistic Regression

(a) Logistic regression with variables identified in univariate analysis							
Variables in the Equation							
		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1 ^a	Previous history of depression	2.34	1.01	5.33	1	0.02	10.37
	Tobacco use disorder	20.65	7122.14	0.00	1	0.99	928,885,813.88
	Previous history of hypertension	19.60	7122.14	0.00	1	0.99	324,787,187.14
	Constant	-21.82	7122.14	0.00	1	0.99	0.00
^a Variable(s) entered on step 1: Previous history of depression, Tobacco use disorder, Previous history of hypertension. Exp(B) = OR							
(b) Logistic regression in all patients, with “previous history of depression”; relevant variable finally identified							
Variables in the Equation							
		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1 ^a	Previous history of depression	2.89	0.91	10.02	1	0.00	18.00
	Constant	-3.05	0.72	17.70	1	0.00	0.05
^a Variable(s) entered on step 1: Previous history of depression. Exp(B) = OR							
(c) Logistic regression in male patients, with “previous history of depression”; relevant variable identified							
Variables in the Equation ^a							
		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1 ^b	Previous history of depression	3.74	1.10	11.62	1	0.00	42.00
	Constant	-2.64	0.73	13.00	1	0.00	0.07
^a Gender: male. ^b Variable(s) entered on step 1: Previous history of depression. Exp(B) = OR							

be considered as a positive result, such factor being relatively easy, quick and costless to assess.

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