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Clinical utility of chosen factors in predicting post-stroke depression: a one year follow-up

Hubert M. Wichowicz[1], Dariusz Gąsecki[2], Piotr Lass[3], Jerzy Landowski[1], Małgorzata Świerkocka[2], Grzegorz Wiśniewski[4], Waldemar N. Nyka[2], Alina Wilkowska[1]

[1]Clinic of Psychiatric Disorders and Neuroses, Chair of Mental Health, Medical University of Gdansk

[2]Clinic of Adult Neurology, Medical University of Gdansk

[3]Department of Nuclear Medicine, Medical University of Gdansk

[4]Graduate Entry Medical School, University of Limerick, Limerick, Ireland

Summary

Aim. The aim of the study was to identify possible interrelation between the presence of post-stroke depression (PSD) and chosen clinical and demographic parameters.

Method. Initially 116 patients (61.4 ± 12.6 years, women N = 42) hospitalized in Neurology Department, Medical University of Gdańsk (April 2003 – December 2005) due to first ischemic stroke, were included in the study. We analysed demographic data, the lesion's side and location according to neuroimaging and global neurological deficit estimated on the first day after the stroke and at discharge using NIHSS (*National Institutes of Health Stroke Scale*) and Barthel Index of Activity of Daily Living.

Psychiatric evaluation was done: 6 (42 ± 3 days) and 12 weeks (84 ± 7 days), as well as 6 (±14 days) and 12 months (±14 days) after stroke based on ICD-10 and functional assessment scale (Rankin Scale).

Results. Depression was diagnosed in 29 patients (27.6%). No correlation was found between PSD and sex or age. On the first day and at discharge patients without PSD were functioning slightly better but the difference was not statistically significant. We found association between the presence of PSD and the results of Rankin scale with the exception of degree of improvement during whole observation. In the group of patients with PSD left hemisphere strokes were slightly more common, but the difference did not reach statistical significance. The location of lesions in frontal lobes and basal ganglia was associated with presence of depression.

Conclusions. We found the association between the presence of PSD and location of lesions (frontal lobes or basal ganglia), as well as with the degree of functional improvement during 12 months after stroke.

Key words: post-stroke depression, computed tomography, magnetic resonance

Introduction

Identifying group with higher risk of post-stroke depression (PSD) among patients after stroke would definitely allow more effective prevention and earlier treatment [1, 2]. According to meta-analysis by Hackett and Anderson published in 2005, 87 factors can be distinguished and all of them deserve further evaluation. Present studies regarding risk factors for PSD suggest that only three of them are well established: the level of functioning, severity of stroke and presence of cognitive impairment. Loneliness and luck of social support can also have some prognostic value [3]. Five years later Robinson and Spelletta in their review of studies on PSD conducted during last 20 years came to similar conclusions (MEDLINE and PubMed, 2,905 results) [4]. The newest meta-analysis published in 2013 showed the same results, adding two factors: anxiety and depression in medical history [5].

The most discussed risk factor for post-stroke depression is hypothesis connecting left hemisphere stroke with PSD. Starting in 1984 Robinson et al. tried to prove that left hemisphere stroke, especially localized in frontal lobe is associated with higher risk of PSD [4, 6–8]. However, most of the studies, including based on large number of patients or meta-analyses, did not confirm this hypothesis [9–14].

Only few Polish papers examined frequency of depression after stroke and risk factors. In the first one, a hospital-based sample of 72 stroke patients was followed up for 6 months after stroke, 46% of them had depression diagnosed by Zung Scale [15]. In 2007 J. Białkowska and B. Idzikowska observed 67 rehabilitation-based patients for 9 months, 10 patients suffered from depressions assessed using Geriatric Depression Scale (GDS); prognostic factors were not assessed [16].

Cognitive functions and side of lesion were most frequently examined potential risk factors in Poland. Nowakowska et al. in 2009 examined cognitive functions in 52 patients and in 50% of them the authors recognised sever depressive symptoms (using Beck Depression Inventory, BDI), correlating with left hemisphere lesion, but not with cognitive dysfunction. The authors highlight that all the included patients with stroke had right hemiparesis and some of them had also symptoms of aphasia which was connected with their worse somatic condition [17]. Borkowska et al. included 42 patients with stroke and found worse cognitive functioning in cases of left hemisphere lesion which correlated with the presence of depression diagnosed using Hamilton Depression Rating Scale [18]. Sienkiewicz-Jarosz et al. used GDS, the radio of PSD as 82/242. A relation between depression and gender, age, lesion location was not confirmed in the study. Only a relation with socioeconomic factors was confirmed [19].

Polish researchers prefer to use self-report questionnaires or clinical scales than diagnostic criteria of classification systems. Pękala and Sobów, in the meta-analysis of 44 English-language papers, showed that the value of those 3 systems differ depending on type of population [20]. To our best knowledge it is the first Polish paper using classifica-

tion system, till now correlation between PSD and functional state has not been examined before. Also it is the second Polish paper examining population above 100 people [19].

Aim

The aim of this study was to investigate the possible relation between the presence of PSD and chosen clinical and demographic parameters.

The following hypotheses were tested:

1. Selected demographic parameters (female gender, older age of onset) and global neurological deficit after stroke are associated with higher risk of depression.
2. The functioning of patients with PSD is worse compared to patients without PSD.
3. Lesions located in left hemisphere and frontal brain are associated with higher risk of developing depression during 12 months after stroke.

Material

The study group included patients hospitalised between April 2003 and December 2005 at the Department of Neurology of Medical University of Gdansk due to first ischemic brain stroke (referred to as "stroke" further in this paper). According to the definition of stroke the symptoms had to be present for at least 24 hours [21]. The presence, character and location of the lesion were confirmed by computed tomography (CT) and/or magnetic resonance imaging (MRI). Cases of transient ischemic attacks (TIA), haemorrhage strokes and one case of stroke-like symptoms which turned out to be a glioma were excluded. All patients received written information about the study and gave their oral consent. 116 patients were included in the study (mean age was 61.4 ± 12.6 years, range: 24–89 years). There were 42 females (36.2%, 66.5 ± 14.0, 29–89 years) and 74 males (63.8%, 58.5 ± 10.7, 24–80 years) in the study group. This study was approved by Ethical Committee for Research Projects at Medical University of Gdansk. Partial results have been published before [22–24].

Method

At the time of stroke the following data have been recorded:

1. Gender, age of onset, medical history of psychiatric disorders;
2. The location of brain lesion (side and place according to sagittal plane) according to neuroimaging (CT, MRI);
3. Global neurological deficit – assessed twice: during first 24 hours after stroke and about 14 days after stroke i.e. at the time of discharge from the department of neurology or transfer to a rehabilitation centre. The deficit was evaluated with the use of National Institutes of Health Stroke Scale (NIHSS) and Barthel Index of Activity of Daily Living (BI).

NIHSS is a tool used in objective assessment of impairment caused by stroke (level of consciousness, performance of commends, speech, elements of neurological examinations etc.). Range from: 0 (no stroke symptoms) to maximum possible score 42 [25].The Barthel Index is used to measure performance in activities of daily living such as: grooming, getting dressed, eating etc. First version scored from 0 (completely dependent) to 20 (completely independent) was used [26].

Psychiatric evaluation was done (H.M.W.): 6 (42 ±3 days), 12 weeks (84 ±7 days) and 6 (± 14 days) and 12 months (±14 days) after stroke. If patients or their relatives asked there was a possibility of pre-schedule an appointment.

Depression diagnosis was set according to ICD-10 criteria, also Hamilton Rating Scale for Depression (HRSD) was used. Additionally, Modified Rankin Scale was used to assess the level of functioning. It is a simple, short scale for measuring the degree of disability. The scale runs from perfect health without symptoms (0), through no significant disability (carrying out all usual activities), slight, moderate, moderately severe disability to severe disability (5), with necessity of constant nursing care [27].

Excluding criteria at the later phase of the study were:

1. Lack of consent for psychiatric evaluation from the patients or their closest relatives;
2. Occurrence of additional serious medical condition which could be associated with developing depression like: second stroke, myocardial infarction occurring at the period of observation, newly diagnosed or relapsed neoplasm;
3. Lost track of the patient or his death.

Five patients died before the first evaluation. 6 patients (1 with diffused neoplastic disease, 3 withdrew their consent, 2 in severe psychosomatic condition precluding ICD-10 diagnosis). Finally 105 patients were included, another 4 were excluded from CT/MRI results analysis as they were either both-handed or left-handed.

For statistical analysis Statistica PL version 7.1 was used.

Results

In 17 cases patients or relatives asked for pre-schedule the appointment, in all cases it took place before the first appointment, in 4 cases PSD was diagnosed. Table 1 contains data concerning the severity and course of PSD during subsequent visits.

Table 1. **Prevalence and severity of PSD during subsequent visits**

		Visit 1	Visit 2	Visit 3	Visit 4
Number of cases	Mild	10	11	10	1
	Moderate	12	4	1	3
	Severe	2	0	0	0
New cases		24*	1	3	1
Improvement (with respect to the preceding visit)		-	9	5	8
Worsening (with respect to the preceding visit)		-	1	0	2
HDRS mean value ± standard deviation	PSD(+)	17.0 ± 6.8	11.1 ± 5.2	10.5 ± 5.4	10.1 ± 5.9
	PSD(-)	6.6 ± 5.2	5.2 ± 4.7	4.7 ± 5.1	3.3 ± 3.1

*4 cases of pre-schedule appointments

The vast majority of cases of depression (83%) had onset during the first 3 months after stroke, then there were few cases of milder severity. Treatment was offered to all patients with depression, 27 (93%) patients agreed for treatment. Following agents were prescribed: sertraline (respectively: N = 11), paroxetine (8), fluoxetine (3), mianserin (3), citalopram (1) and fluvoxamine (1). 83% patients suffering from PSD had full antidepressant therapy; three patients (sertraline 2, paroxetine 1) without full compliance (data from relatives).

No statistically significant difference was found in gender (Yates' χ^2: $\chi^2 = 0.292$; df = 1; p =).589) and age (PSD (+) 61.3 ± 10.0 vs. PSD (-) 60.3 ± 13.3 years). Three patients (2 females) were diagnosed with depression before. In none of these cases preventive treatment was used. Two patients suffered from epilepsy (both of them were males), one of them used antiepileptic drugs. Another 2 patients developed epilepsy after stroke. Possible effect of excluding them would be minimal; therefore they were included in the final statistical analysis.

We did not confirm statistically significant influence of clinical status of patients (BI and NIHSS administered on the day of stroke and at discharge) on developing post-stroke depression. Patients without PSD, however, functioned slightly better on the day of stroke and at discharge (Table 2). Notice that NIHSS and BI have opposite ratings. The worse clinical state is associated with higher NIHSS and lower BI score.

Table 2. **The values (mean ± standard deviation) describing neurological deficit and level of functioning on the day of stroke and at discharge (14 days after stroke)**

	Day of stroke		Day of discharge	
Scales:	NIHSS	BI	NIHSS	BI
PSD(+)	10.4 ± 6.2	8.1 ± 8.4	4.9 ± 4.6	11.3 ± 8.5
PSD(–)	8.4 ± 6.1	11.5 ± 8.0	4.2 ± 4.7	13.8 ± 7.8
P	0.112	0.079	0.258	0.183

P: Mann-Whitney U test PSD(-) vs. PSD(+)

Clear association was found between the presence of PSD and Rankin Scale ratings during 12 months of observation. However, the difference in rating between first and last visit (degree of improvement) was independent of the presence of PSD (Table 3).

Table 3. **The level of functioning (mean ± standard deviation) according to Rankin scale during 12 months of observation and degree of improvement in both groups PSD(-) and PSD(+)**

	PSD(-)	PSD(+)	P
Visit 1	2.4 ± 1.3	3.3 ± 1.1	0.006
Visit 2	1.9 ± 1.3	2.6 ± 1.1	0.021
Visit 3	1.8 ± 1.3	2.5 ± 1.1	0.022
Visit 4	1.7 ± 1.2	2.5 ± 1.2	0.017
Diference between visits 1 and 4	0.81 ± 0.73	0.77 ± 1.07	0.646

P: Mann-Whitney U test PSD(-) vs. PSD(+)

Examining the relationship between PSD and stroke side, we initially compared the functional state during the year of observation between: left-, right – and both side strokes. No significant association was found between the side of lesion and maximum rating in Rankin scale recorded during 12 months of prospective observation (Kruskal-Wallis test: $H = 4.204$; $df = 2$; $p = 0.122$, without detailed presentation of result). Therefore, our patients were not a group charged with more severe course of left hemisphere stroke, such as in the cited study by Nowakowska et al. [17].

In the group of patients with depression left-hemisphere strokes were slightly more prevalent (Table 4). However, the percentage was not large enough to cause statistically significant difference in distribution on estimated level of significance (Pearson's χ^2: $\chi^2 = 1.753$; $df = 2$; $p = 0.208$, for the whole table; $\chi^2 = 1.746$; $df = 1$; $p = 0.093$ left-hemisphere stokes vs. others; one-tailed test).

Table 4. **Presence of PSD and the side of stroke lesion (N = 101)**

Side of stroke lesion	Left hemisphere	Right hemisphere	Both sides	Total
PSD(-)	42 (66.6%)	22(78.6%)	8 (80.0%)	72
PSD(+)	21 (33.3%)	6 (21.4%)	2 (20.0%)	29
Total	63 (100%)	28 (100%)	10 (100%)	101

Table 5 contains number of patients with depression and location of stroke lesion (more often lesions) according to sagittal plane.

Table 5. **The presence of PSD and the location of stroke lesion in certain brain structures according to sagittal plane (N = 101), the percentage concern number of patients from PSD(+) and PSD(-) subgroups**

	Number of patients in the group N (%)				χ^2	P
	PSD(-). N=72		PSD(+). N=29			
	With lesions	Without lesions	With lesions	Without lesions		
Frontal lobes	23 (31.9%)	49 (68.1%)	18 (62.1%)	11 (37.9%)	7.780	0.005
Temporal lobes	27 (37.5%)	45 (62.5%)	13 (44.8%)	16 (55.2%)	0.464	0.496
Occipital lobes†	23 (31.9%)	49 (68.1%)	7 (24.1%)	22 (75.9%)	0.287	0.592
Parietal lobes	26 (36.1%)	46 (63.9%)	12 (41.4%)	17 (58.6%)	0.244	0.621
Basal ganglia†	19 (26.4%)	53 (73.6%)	15 (51.7%)	14 (48.3%)	4.862	0.027
Thalamus ††	4 (5.6%)	68 (94.4%)	0 (0%)	29 (100%)		0.322
Cerebellum/ Brainstem ††	1 (1.4%)	71 (98.6%)	1 (3.4%)	28 (96.6%)		0.494

P: Pearson's χ^2 test with the exception of: † χ^2 test with Yates' correction, †† Fisher's exact test two-tailed

Lesions located in frontal brain and basal ganglia in CT/MRI were associated with more frequent presence of depression. Including the side of lesion as an additional variable to data from Table 5 did not increase the p value.

Discussion

This study is 1-year prospective observation based on acute inpatient sample sample after first ischemic stroke, without additional inclusion criteria. Methodology is similar to Italian study DESTRO, though there is a slight difference (DESTRO: the last visit after 2 years, presence of haemorrhagic strokes, although only 10%) [28]. Recently similar methodology was used by Belgians, in the first paper which presented PSD ratio during three months of observation after stroke (28.1%) [29].

It is suggested that the highest percentage of PSD in stroke survivors is presented in rehabilitation-based samples, and the lowest in population based samples [30]. 27.6% of patients were identified as suffering from PSD. Our results are consistent with meta-analyses (Robinson: 16–47% [31], Hackett et al.: 1/3 [32]). Our result, places in the

middle of suggested values, matches up with this rule and are consistent with another research citied here [28, 29, 33–35].

PSD may potentially start in different period after stroke and depending on period of onset may be connected with different risk factors [30]. Åström et al. found that in one of the first papers concerning PSD (N = 80, 3-years observation). The most important predictors of immediate major depression were: left frontal lobe lesion, dysphasia, and living alone, therefore both biological and psychosocial factors. In 3rd month after stroke, a psychosocial factor: dependence in activities of daily living became the most important predictor. Next the role of psychosocial factors increased till 3 years after stroke, when biological factor (cerebral atrophy) again gained in importance. The highest prevalence of PSD (31%) was during first 3 months after stroke and after one year half of them was in remission [33]. Data from patients registered in the South London Stroke Register (1995–2009, N = 4022, 15-years observation) also reported onset of PSD within 1 year after stroke, mostly within 3 months. The authors pointed dynamic course of PSD, after 1 year most of depressive patient recovered, but there was a high risk of recurrence [34]. DESTRO (N = 1064) similarly reported that 80% of PSD onsets took place within 3 months after stroke [28]. By contrast, the Sunnybrook Stroke Study (N = 436) reported stable rate of depression during 1 year observation [35], alike the meta-analysis by Ayerba at al [5]. The last one completely omitted treatment. Our study confirms data about early onset of the most PSD episodes. Within 6 weeks 24/29 episodes were started, then the number of new episodes was small, not proper to analysis. We also confirm tendency to improvement in patient's mental condition.

Gender (female) initially was seen as a factor of PSD, similarly to "primary" affective disorder. But early data did not confirm this theory [33, 36], moreover, lack of women predominance was suggested as a proof of etiological difference of PSD [37]. Meta-analyses based on the largest number of patients also did not confirm gender as a risk factor [3, 4]. But recently again a lot of papers were published, where this relation was reported [38, 39], moreover, meta-analysis of 24 papers (1995–2012) also suggested this correlation [40]. Our results do not confirm this, gender is not a risk factor, as well as age, for the results are also inconsistent.

As far as two consecutive factors: the degree of physical impairment and stroke severity (both confirmed by meta-analyses [3–5]), our study confirmed that only the first one is associated with PSD. The second one: severity of stroke (understood as global neurological deficit) which was evaluated on the day of stroke and at discharge turns out to be worse in the group of patients who developed PSD later (NIHSS, BI), but the difference was not statistically significant.

The result regarding degree of functional improvement can be surprising. Degree of improvement measured with Rankin Scale in the group with PSD was only 5% lower (not significant) compared to the group without depression. It seems contrary

to robust evidence concerning negative effect of PSD on rehabilitation [35, 41–44] and even survival [45]. However, we should keep in mind that majority of patients were treated with relevant doses of antidepressants and psychiatric condition improved in most cases. Not only the number of patients suffering from PSD decreased from 24 (visit 1) to 5 (last visit), but also severity of depression in the remaining group decreased significantly (Table 1). This result suggests that treatment of PSD can increase chances for functional improvement comparable to the improvement observed in subjects without depression.

Side location and PSD is a problem with few meta-analyses, with contradictory results. Chronologically: Agrell and Dehlin (1994, 25 studies) and Singh et al. (1998, 12 studies) in their meta-analyses showed that a slightly higher number of reports indicate a higher incidence of PSD in left-side strokes [9, 12]; The most frequently cited meta-analysis by Carson et al. (2000, 35 studies) did not demonstrate the existence of correlation between side of stroke and PSD or sometimes suggested correlation with the distance from the sagittal plane [11]; Narushima et al. (2003, from potentially 356 studies, only 14 (sic!) were included) proved the existence of correlation between left-side stroke and PSD; Bhogal et al. (2004, 26 studies) also proved this correlation, but only regarding hospitalised population [7, 10]. Yu et al. (2004, N= 3668, 52 studies) showed low correlation with right hemisphere stroke. Authors point out the bias of most studies: exclusion of patients with speech dysfunction, and thus with left-side strokes [14]. The newest one: Wei et al. (2014, N = 5,507, 43 studies) again showed low correlation with right hemisphere stroke, but only for patients with onset at acute phase [13]

To summarize, the results of published studies suggest that if there is any correlation between the left side of the stroke lesion and PSD, it is very weak and usually does not reach statistical significance. Our results support this observation.

In this study location of stroke lesions in the frontal lobes and basal ganglia is more common in people with PSD. Many studied refer to the frontal lobes as the structure import in pathology of PSD, some previously mentioned meta-analysis discuss it (e.g. [4, 11]). In the presented study significance of damage of these structures in PSD was confirmed.

Frontal areas are connected to basal ganglia which are considered to be a part of the structures and circuits associated with mood. The role of their damage in the pathogenesis of PSD is still outside the mainstream of research on the significance of the location of stroke lesions. However, already meta-analysis by Bhogal et al. from 2004 suggested a correlation between left basal ganglia lesions and PSD, quoting 3 early publications [10]. It should be emphasized that all these works have investigated the occurrence of depression short after stroke (up to 2 months), as described in this paper, the majority of cases of depression occurred in the period up to 3 months after the cerebral incident. Additionally, in 2004 Finnish paper reported on the importance of damage to the basal ganglia in PSD. Using MRI, he reported a significant role of

damage to deep structures in the later occurrence of PSD, also within 3 months after stroke (odds ratio OR = 7.2), highlighting the increasingly important of left-sided lesions. In the commentary, the authors emphasize the role of disruption of fronto-subcortical connections [46].

In 2007 Japanese researchers, on the basis of their clinical material (N = 126 with PSD/243), came up with the concept of two dimensions of PSD (affective and apathetic) and basal ganglia damage was associated with apathetic depression [47]. Six years later, they described another 149 cases of PSD, where again the location of changes in the basal ganglia correlated with apathetic depression [48]. The importance of any location of injury to a development of apathy as an isolated symptom of stroke was not confirmed by so far the only meta-analysis of this symptom (19 studies, N = 2,221) [49]. The presented material confirms a statistically significant higher number of people with basal ganglia lesions among patients with PSD.

Methodological limitations

1. In the case of PSD the problem is not lack, but excess of studies. The used methodology is often incomparable, and sometimes even the results are completely contradictory. In addition, a large number of co-factors is potentially worth examining. Each study must have some limitations, because it is practically impossible to analyse even all the most important factors in a single study.
2. Many clinical data have been omitted here. The most important is the lack of volumetric assessment of the lesion and not taking into account in the initial state diseases potentially resulting in depression, such as ischemic heart disease. The data associated with the time between the stroke and the beginning of PSD have not been analysed.

The first limitation resulted from the conduct of the study. Initially, patients were diagnosed according to the procedure adopted in the Department of Neurology, partly by CT partly by MRI, therefore it was difficult to collect standardized data. For the second it is sporadic to meet stroke patient with unloaded condition. Over 90% of patients showed at least one component of the metabolic syndrome, the severity of atherosclerotic lesions in this group was high, with a potential risk for an episode of depression. Analysis of the data on the time range between stroke and the beginning of PSD has been skipped due to the small number of cases (only 5) in which depression occurred in a period longer than 3 months after the stroke.

Conclusions

1. The level of global neurological deficit at the time of stroke as well as patient's gender and age of onset did not relate significantly to increased risk of post-stroke depression.
2. Patients with post-stroke depression are characterised with worse functioning after stroke.
3. Location of stroke lesion in the frontal part of the brain (frontal lobes) or deep brain structures (basal ganglia) is associated with higher risk of depressive episode during the first year after stroke. No statistically significant association was found between left-hemisphere stroke and a presence of post-stroke depression.

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Address: Hubert M. Wichowicz
Clinic of Psychiatric Disorders and Neuroses
Chair of Mental Health
Medical University of Gdansk
08-952 Gdańsk, Dębinki Street 7