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# Factors associated with pre-stroke dementia

## The Cracow Stroke Database

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**Abstract** *Background* Many stroke patients who fulfilled diagnostic criteria for dementia three months after stroke had a mental deterioration before stroke, implying an underlying neurodegenerative process. The goal of this study was to determine the factors associated with pre-stroke dementia in hospitalised-based population. *Subjects and Methods* Pre-stroke cognitive decline was evaluated in 250 stroke patients using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Patients with IQCODE score ≥104 were classified as having pre-stroke dementia. Clinical, radiological, and biochemical data of patients with and without pre-stroke dementia were compared. *Results* Pre-stroke dementia was found in 12 % of 250 stroke patients. Patients with pre-stroke dementia were older, suffered more frequently from ischemic heart disease and diabetes, and had more frequently prior cerebrovascular disease. These patients had significantly more brain atrophy and number of old infarcts on CT than patients without pre-stroke dementia. Serum γ-globulins levels at admission were significantly higher in patients with pre-stroke dementia. In logistic regression analysis female gender (OR 3.47, CI 95 % 1.25–9.64), history of previous stroke (OR 3.46, CI 95 % 1.26–9.51), the number of old infarcts on CT (OR 1.58, CI 95 % 1.08–2.33) and serum γ-globulins level (OR 1.19, CI 95 % 1.02–1.40) were independently associated with pre-stroke dementia. *Conclusions* Female gender and previous ischemic stroke are the most important determinants of pre-stroke cognitive decline.

**Key words** stroke · dementia · risk factors

## Introduction

One tenth to one sixth of patients admitted to the hospital after an acute stroke have pre-existing dementia [21]. Taking into account the preventive strategy, it is important to identify the factors associated with pre-stroke dementia (PSD). There are only three studies [4, 8, 18] with the primary objective of determining the factors predicting PSD and only in two of them was pre-stroke dementia diagnosed in the acute stage of stroke [5, 12].

So far the following independent factors associated with PSD have been found as independent factors associated with PSD: female gender [5, 11], low education [5, 26], history of previous stroke [5, 26], family history of dementia [11], cerebral atrophy [5, 11, 26], leukoaraiosis [26] and medial temporal lobe atrophy [12, 26].

Recently we have shown that the incidence of pre-stroke dementia in a hospitalised Polish population is 12 % [17]. The aim of this study was to determine the factors associated with PSD. Besides demographic data, vascular risk factors, clinical and radiological stroke fea-

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tures we have analysed also the significance of basic biological parameters, including inflammatory markers (erythrocyte sedimentation rate; white cell count; gamma-globulin fraction). Although there is strong evidence indicating that inflammatory reaction can be involved in the pathogenesis of different types of dementia [1], the role of routine biochemical markers of inflammation as predictors of stroke-related dementia was not addressed in previous studies.

## Subjects and methods

Subjects for this study were recruited from among patients admitted consecutively to the Department of Neurology, Jagiellonian University, Cracow, Poland, from 1 January 2000 to 30 March 2001. Eligible patients were aged 40 years or older and had had an ischemic or hemorrhagic stroke. Patients with a transient ischemic attack, a subarachnoid haemorrhage, a stroke associated with another primary brain lesion (e. g. tumor, trauma) as well as patients without a reliable informant or transferred from another hospital were excluded.

Finally, from 292 consecutive patients, 250 patients (73.9 %) fulfilled the recruitment criteria (mean age: 67.5 ± 11.8 years; 54.8 % men). Thirty-two patients had an intracerebral hemorrhage and 218 had an ischemic stroke. The detail description of enrolled patients has been given elsewhere [17].

The demographic data, history of previous disease and habits, vascular risk factors and biochemical data at admission were recorded.

Arterial hypertension was diagnosed if the patient was taking antihypertensive drugs before stroke onset or if ≥ 2 readings of blood pressure of ≥140 mmHg (systolic) or ≥ 90 mmHg (diastolic) were documented in medical records before the onset of stroke or persistently observed during admission after the acute phase of stroke. Diabetes mellitus was diagnosed if a patient had a history of diabetes mellitus that was confirmed by their medical records or was taking insulin or an oral hypoglycaemic agent. Obesity was defined as body mass index > 30 kg/m$^2$. Peripheral vascular disease was diagnosed when a patient had a history of calf pain induced by exercise or if a patient was subjected to positive angiography or vascular surgery. A smoker was defined as one who had a history of cigarette smoking during the last 5 years.

Neurological deficit at admission was assessed using the Scandinavian Stroke Scale [19] and functional outcome using the Barthel Index [21] and the Rankin Scale [28] at discharge from the hospital.

Stroke subtypes (total anterior circulation infarction – TACI, partial anterior circulation infarction – PACI, lacunar infarction – LACI, posterior circulation infarction – POCI) were defined according to the Oxfordshire Community Stroke Project [3].

Every patient underwent CT within 24 h after onset of symptoms. Cerebral atrophy was scored as following: no atrophy = 0, mild atrophy = 1, moderate atrophy = 2, and severe atrophy = 3. The presence of leukoaraiosis and a number of old infarcts were recorded. We defined old infarcts as infarcts seen at admission on CT scans and not related to the index stroke (both silent infarcts defined as old infarcts found in patients without history of stroke and previously clinically manifesting infarcts).

The assessment of PSD was conducted within 48 h of stroke onset using a Polish translation of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [15]. This method detects a fall from a higher to a lower intellectual level [13, 14]. The informant completing the questionnaire was required to have known the patient for at least 10 years prior to admission with regular contact defined as interacting together at least once a week. Patients with IQCODE score ≥104 were classified as having PSD.

All patients or patients' close relatives gave informed consent prior to their inclusion in the study.

Patients were divided into 2 groups: with and without PSD. As most continuous variables showed significant departures from normality, the nonparametric Mann-Whitney's U test was used for them instead of ANOVA. The $\chi^2$ test was used for dichotomous and other categorical variables. All variables with $P < 0.1$ in the univariate analysis were included in a multivariate analysis with a backward stepwise logistic regression to identify independent predictors of PSD. Before the logistic regression was applied, multicolinearity among selected variables was assessed by means of Pearson's r in the case of the relationship between continuous variables and continuous versus dichotomous variables. The phi coefficient was used to assess the correlation between dichotomous variables. No colinearity was detected, as the highest correlation was only 0.67, in the case of relationship between hematocrit and hemoglobin. To control for age and gender, both these variables were included in the regression model, although only gender proved significant in univariate analyses looking for differences between demented and not demented patients. The odds ratios and 95 % confidence intervals were estimated from the regression coefficients. $P < 0.05$ was considered as significant. The analysis was performed using SPSS for Windows v. 10.0 (SPSS Inc, Chicago, IL).

## Results

Pre-stroke dementia was found in 12 % (95 % CI 11.6 %–12.04 %) of the 250 patients.

Demographic characteristics of patients with and without PSD are shown in Table 1.

Patients with PSD were significantly older than patients without PSD. Patients with PSD were more frequently women than patients without PSD (60 % vs 43.2 %), however, this difference was not significant ($P = 0.08$).

Vascular risk factors in patients with and without PSD are shown in Table 2.

Patients with PSD suffered from ischemic heart disease and diabetes mellitus more frequently and had previous stroke more often than patients without PSD.

Clinical and radiological stroke features in patients with and without PSD are shown in Table 3.

Patients with PSD had more severe neurological deficit on admission and worse outcome than patients without PSD.

Patients with PSD had significantly more brain atrophy and a number of old infarcts on CT than patients without PSD.

**Table 1** Demographic data in patients with and without PSD

| | Not demented (n = 220) | Demented (n = 30) | p |
|---|---|---|---|
| Mean age (years) (SD) | 66.5 (11.0) | 73.2 (12.8) | 0.003 |
| Men | 125 (56.8 %) | 12 (40 %) | 0.083 |
| Education | | | 0.118 |
| Elementary school | 96 (43.6 %) | 18 (60 %) | |
| Other[1] | 124 (56.4 %) | 12 (40 %) | |

[1] Vocational school, High school, University

**Table 2** Vascular risk factors in patients with and without PSD

| | Not demented | Demented | p |
|---|---|---|---|
| Arterial hypertension | 168 (76.4%) | 25 (83.3%) | 0.393 |
| Ischemic heart disease | 120 (54.5%) | 24 (80.0%) | 0.008 |
| Myocardial infarction | 34 (15.5%) | 3 (10.0%) | 0.430 |
| Atrial fibrillation | 39 (17.7%) | 8 (26.7%) | 0.240 |
| Cardiac valvulopathy | 17 (7.7%) | 0 (0.0%) | 0.115 |
| History of previous stroke | 37 (16.8%) | 13 (43.3%) | 0.002 |
| Diabetes mellitus | 46 (20.9%) | 15 (50.0%) | 0.001 |
| Cigarette smoking | 69 (31.4%) | 9 (30.0%) | 0.880 |
| Alcohol consumption | 20 (9.1%) | 3 (10.0%) | 0.872 |
| Obesity | 60 (27.3%) | 8 (26.7%) | 0.994 |
| Transient ischemic attacks | 15 (6.8%) | 4 (13.3%) | 0.207 |
| Migraine | 8 (3.6%) | 0 (0.0%) | 0.228 |
| Peripheral vascular disease | 52 (23.6%) | 3 (10.0%) | 0.091 |

Biological data in patients with and without PSD are shown in Table 4.

Patients with PSD had a significantly higher serum level of γ-globulins than patients without PSD. There was a significant trend showing lower hematocrit and hemoglobin in patients with PSD (P = 0.07 and P = 0.06, respectively).

The following variables were found as independently related to PSD on multivariate analysis: female sex (OR 3.47, CI 95 % 1.25–9.64, P = 0.017), history of previous ischemic stroke (OR 3.46, CI 95 % 1.26–9.51, P = 0.016), a number of old infarcts on CT (OR 1.58, CI 95 % 1.08–2.33, P = 0.020), and serum γ-globulins level (OR 1.19, CI 95 % 1.02–1.40, P = 0.033). The degree of brain atrophy showed a trend to be a risk factor for PSD. However, significance was not reached (OR 1.62, CI 95 % 0.96–2.74, P = 0.073).

The overall p for the whole model was less than 0.001. The Nagelkerker's R-square was 0.30.

## Discussion

Pre-stroke dementia is found in 9.6 %–16.3 % of stroke patients [22].

Previous studies pointed out that the factors predicting pre-stroke dementia are reminiscent of both degenerative and vascular brain pathology.

With respect to vascular factors, we found that a history of a previous stroke and a number of old infarcts on CT are predictors of PSD. Similarly Pohjasvaara et al. [26] and Barba et al. [5] showed that a history of previous stroke is an independent risk factor of PSD.

With respect to neurodegeneration-related factors, female gender was significantly associated with PSD. This finding is in accordance with previous observations of higher prevalence of dementia among women [6].

In univariate analysis the degree of brain atrophy correlated with PSD, albeit on multivariate analysis this relationship did not reach the level of significance. Poh-

**Table 3** Clinical and radiological stroke features in patients with and without PSD

| | Not demented | Demented | p |
|---|---|---|---|
| Ischemic stroke | 191 (86.8) | 27 (90 %) | 0.40 |
| Leukoaraiosis | 71 (32.3 %) | 14 (46.7 %) | 0.118 |
| Vascular territory of stroke | | | 0.270 |
| Anterior circulation | 150 (80.6 %) | 25 (89.3 %) | |
| Posterior circulation | 36 (19.4 %) | 3 (10.7 %) | |
| Ischemic stroke subtypes | | | 0.270 |
| TACI | 24 (11 %) | 6 (20 %) | |
| PACI | 112 (51.1 %) | 18 (60 %) | |
| LACI | 25 (11.4 %) | 3 (10 %) | |
| POCI | 36 (16.4 %) | 2 (6.7 %) | |
| Not classifiable | 22 (10 %) | 1 (3.3 %) | |
| Mean SSS score on admission (SD) | 45.5 (15.5) | 36.9 (18.0) | 0.003 |
| Mean Barthel Index on discharge (SD)[1] | 76.8 (29.4) | 57.9 (34.5) | 0.004 |
| Rankin Scale on discharge[1] | | | 0.019 |
| Low Rankin Scale (0–2) | 138 (65.7 %) | 12 (42.9 %) | |
| High Rankin Scale (3–5) | 72 (34.3 %) | 16 (57.1 %) | |
| Mean number of old infarcts on CT (SD) | 1.0 (1.0) | 1.9 (1.6) | < 0.001 |
| Degree of brain atrophy – mean (SD) | 1.09 (0.88) | 1.7 (0.99) | 0.001 |

[1] The Barthel and Rankin Scales are presented in the Table 3, as they are important variables in research on dementia. However, they were not included in the final regression analyses, because they were scored on discharge, and therefore could not be predictors of the pre-stroke dementia

**Table 4** Biochemical date of patients with and without PSD on admission

| | Not demented (SD) | Demented (SD) | p |
|---|---|---|---|
| Haemoglobin (g/dL) | 12.8 (1.5) | 12.3 (1.9) | 0.065 |
| Haematocrit (%) | 37.6 (5.3) | 35.8 (7.3) | 0.074 |
| White blood count ($10^9$/L) | 8247.3 (3973.8) | 9065.3 (3908.1) | 0.222 |
| Erythrocyte cell sedimentation rate (mm/h) | 29.2 (23.1) | 37.4 (32.5) | 0.347 |
| Creatinine (mg/dL) | 80.8 (31.8) | 87.7 (44.8) | 0.368 |
| Glucose (mmol/L) | 7.0 (3.0) | 7.8 (2.9) | 0.097 |
| Protein level (g/L) | 69.1 (6.0) | 69.4 (7.1) | 0.944 |
| Albumin fraction (g/L) | 37.8 (5.2) | 37.1 (5.2) | 0.363 |
| Gamma globulin fraction (g/L) | 11.0 (2.8) | 12.4 (3.0) | 0.021 |
| Fibrynogen (g/L) | 3.4 (1.6) | 4.4 (5.3) | 0.214 |
| LDL-cholesterol (mg/dL) | 3.4 (1.0) | 3.2 (1.1) | 0.399 |
| HDL-cholesterol (mg/dL) | 1.4 (0.4) | 1.4 (0.5) | 0.551 |
| Triglyceride-cholesterol (mg/dL) | 1.5 (1.0) | 2.1 (3.9) | 0.799 |

jasvaara et al. [26] found that both cortical atrophy (frontal, entorhinal, hippocampal, and medial temporal lobe atrophy) and central atrophy (temporal, frontal, lateral and occipital region atrophy) are related to PSD in univariate analysis. However, in the multiple logistic model, only medial temporal cortical atrophy (MTCA) remains an independent predictor of pre-stroke dementia [26, 12]. The authors of recently published studies have shown that MTCA reflects a different pathogenic process and is not specific for Alzheimer's disease but it is also observed in vascular dementia [8, 23, 24]. We cannot confirm those results because we assessed only global atrophy without special analysis of the medial temporal lobe region.

So far only one study has demonstrated that leukoaraiosis independently predicts PSD in multivariate model [11]. We were not able to confirm this observation. In contrast to the mentioned study we assessed only the presence or absence of leukoaraiosis without grading its extent.

The type of stroke data bank is very important for assessing risk factors for pre-stroke dementia. Hospital-based studies tend to include more severe strokes and those occurring in younger populations and those having a higher mortality. Therefore, selection bias may influence the results. Because our Stroke Unit serves as a community hospital as well as referral hospital we excluded patients transferred from other hospitals to avoid this bias. The mean age of patients with stroke in our study is 67.5 ± 11.8 years. It was found that the mean age of patients with stroke admitted to the hospital in South Poland is 69.8 ( ± 12.4) years [Cracow Stroke Registry-data prepared for publication]. It shows that the mean age of patients with stroke in our study is younger than in other studies [5, 11, 26], that is not due to the hospital bias but rather because of some other factors for example life style, socio-economic status, genetic factors in our country when compared with West European Countries. We believe these factors do not affect the rate of dementia in our stroke cohort.

Vascular disorders are associated with a higher risk of dementia and vascular risk factors are related to other causes of dementia [26]. In our study patients with PSD more often suffered from vascular risk factors than those without dementia. However, myocardial infarction, cardiac valve disease and peripheral vascular disease were found less often in patients with PSD although the differences were not significant (Table 2). Vascular risk factors are well known predictors of case fatality [16, 20, 27]. Dementia, whatever its etiology, diminishes life expectancy [2, 3, 6, 9, 10]. We think that people sharing these risk factors are even less likely to survive and it can explain the paradoxical lower rate of these risk factors in our group of patients with PSD.

Our finding that an elevated serum level of γ-globulins can modestly, but significantly increase the risk of PSD merits consideration. There are numerous studies showing the involvement of inflammatory markers in pathogenesis of dementia [1]. Gamma globulins belong to acute phase proteins and their synthesis is strongly regulated by interleukin-6 [18]. It was shown recently that high levels of interleukin-6 are associated with a poorer baseline cognitive function and predict increased risk for cognitive decline at the 2.5- and 7-year follow-ups for a cohort of older men and women who were functioning relatively well at the inception of the study [29]. A genetic study also demonstrated that polymorphisms in the interleukin-6 gene that decrease plasma interleukin-6 level may be associated with a lower risk of developing Alzheimer's disease [25]. The issue of the role of chronic inflammatory markers (including interleukin-6 and c-reactive protein) in PSD should be addressed in future studies.

In conclusion: in our study, female gender and previous brain ischemia were the most important determinants of pre-stroke dementia.

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