Determinants of post-stroke cognitive impairment: analysis from VISTA

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Determinants of post stroke cognitive impairment.

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Abstract:

Background: Post stroke cognitive impairment (PSCI) occurs commonly and is linked with development of dementia. It is not clear whether acute stroke factors are associated with development of PSCI. We investigated the relationship between cardiovascular risk factors, stroke symptoms and presence of PSCI at 1 and 3 years after stroke.

Methods: We accessed anonymised data from the Virtual International Stroke Trial Archive (VISTA), including demographic and clinical variables. PSCI was defined as a Mini Mental State Examination (MMSE) score of ≤26. We assessed univariate relationships between baseline stroke symptoms and PSCI at 1 and 3 years following stroke, retaining the significant and relevant clinical factors as covariates in a final adjusted logistic regression model.

Results: We analysed data on 5435 patients. Mean (±SD) age was 62.6 (±12.6) years, 3476 (65%) patients were male. Follow up data were available for 2270 and 1294 at one and three years, respectively. After adjusting for age, stroke severity, hypertension, diabetes and type of qualifying event, initial stroke impairment (leg paralysis) was associated with increased rate of PSCI at one year (OR=1.62; 95% CI=1.20-2.20) and at three years (OR=1.95; 95% CI=1.23-3.09). Associations were consistent on subgroup analysis restricted to ischaemic stroke and transient ischaemic attack (N=4992).

Conclusions: Early clinical features are associated with development of PSCI up to 3 years after stroke, with initial stroke impairment consistently associated with PSCI.

Introduction

Post stroke cognitive impairment (PSCI) represents an important subset of patients with VCI, and refers to patients who develop cognitive deficits after a stroke. Cognitive impairment related to cerebrovascular causes can further progress to dementia[1] which affects up to a third of stroke patients and represents one of the main causes of functional dependency[2,3] and mortality after stroke[4]. Identification of factors associated with PSCI may be valuable to prevent progression of cognitive deficits.

Pendlebury and Rothwell identified demographic and vascular factors as well as imaging features associated with incident dementia after stroke[5]. Characteristics of the stroke event are also associated with subsequent development of PSCI. Severe clinical stroke deficits at onset are associated with higher risk of PSCI[6,7]. No differences have been found between hemorrhagic and ischemic stroke in causing PSCI, although the different survival rate may lead to estimation bias[3]. Moreover, it has been hypothesized that some stroke deficits could *per se* lead to PSCI. Pohjasvaara et al. suggested that aphasia and dominant stroke syndrome are associated with post stroke dementia[8]. However, aphasia is commonly mistaken for PSCI, and even though language represents a cognitive domain, aphasia should not be considered as a surrogate of PSCI. Moreover, relationship between clinical stroke features of the acute event (i.e. stroke symptoms) and cognitive performance are less well described.

The aim of the present study was to investigate the associations between demographical, clinical and stroke features and PSCI in patients with a stroke or transient ischemic attack.

Methods

We conducted a retrospective analysis of individual patient level data from the Virtual International Stroke Trial Archive (VISTA). VISTA is an academic collaboration which provides access to existing patient trial data to perform exploratory analyses with the aim to help planning and design of future clinical trials[9]. Ethical approval was not required since data were anonymised. Our study population included patients with any type of brain vascular event, including ischaemic stroke, hemorrhagic stroke, transient ischaemic attack (TIA). Clinical variables of interest included age, sex, hypertension, diabetes, atrial fibrillation, ischaemic heart disease, hypercholesterolemia, depression (history of), cigarette smoke exposure. Functional status at baseline was assessed with the Oxford Handicap Scale (OHS)[10]. Baseline stroke symptoms included arm paralysis, leg paralysis, sensory deficit, aphasia, neglect, hemianopia dichotomized as presence/absence at stroke onset. All patients underwent global assessment to define stroke subtype, including radiological exams (CT or MR), extensive blood tests, thoracic and neck vessels imaging and cardiac assessment where appropriate.

Cognitive function on survivals at one and three years was assessed on voluntary basis using MMSE, defining cognitive impairment as a score of MMSE≤26[11].

We described characteristics of study population at baseline, one and three years. Furthermore, we described the differences in baseline characteristics of patients for whom MMSE was available and for whom this was not using χ^2 for categorical variables, two-sample t-test for normally distributed variables and Mann-U Whitney test for non-parametric distributions.

We tested univariate associations between cognitive impairment and age, sex, baseline OHS, hypertension, diabetes, arm paralysis, leg paralysis, aphasia, neglect, sensory impairment, hemianopia. We retained significant variables ($p<0.1$) from the univariate analysis in a multivariate logistic regression. We adjusted the analysis for clinical relevant factors such as history of depression and type of brain vascular event. Variables with $p<0.05$ were considered independent predictors of outcomes. Furthermore, we performed subgroup analysis in patients with defined diagnosis of ischaemic stroke and TIA. We accounted for the presence of potential interaction between statistically significant stroke symptoms and functional status at baseline in our multivariate analysis. Analysis was carried out by using SPSS for Windows (version 22.0; SPSS, Armonk NY, IBM Corp.).

Results

Data at baseline were available for 5453 patients, 3476 (65%) were male, mean age (±SD) was 62.5 (±12.5) years. Median time to baseline assessment was 33 days (IQR=8-88) after the qualifying event. After one year, 129 (2.4%) of patients died, and 323 (5.9%) died within 3 years. As to stroke type, 3970 (73%) of patients had ischaemic stroke as qualifying event, around one fifth (1022, 19%) had TIA and 461 (8%) had haemorrhagic stroke (Fig.1).

Table 1 shows baseline characteristics of study population. The majority of patients were functionally independent, with a median OHS of 1 (IQR=1-2). Hypertension was the most frequent cardiovascular risk factor (71%). About two thirds of patients had either arm or leg paralysis, whereas cortical symptoms such as neglect were less frequent (8%).

At one and three years follow up data on MMSE were available for 2270 (41.6%) and 1294 (23.7%) patients, respectively. Patients for whom MMSE scores were available were older ($p<0.001$ at one and three years) and more likely to have less disability at baseline ($p<0.001$ at one and three years). They also had fewer neurological impairment such as aphasia (23% vs 29% at one year, $p<0.001$; 20% vs 28% at three years, $p<0.001$) neglect (6% vs 9% at one and three years, $p<0.001$), arm paralysis (63% vs 73% at one year, $p<0.001$; 63% vs 71% at three years, $p<0.001$) and limb paralysis (53% vs 65% at one year, $p<0.001$; 53% vs 63% at three years, $p<0.001$) (Suppl. Tab.1 and suppl. tab.2). At one year, 781 (34%) patients had MMSE≤26, at three years 391 (30%) had MMSE≤26.

After any brain vascular event age, female sex, stroke severity at baseline, diabetes were independently associated with poorer MMSE at both one and three years (Tab.2). Leg paralysis was also associated with MMSE≤26 at both time points (OR=1.62; 95% CI=1.20-2.20; OR=1.95; 95% CI=1.23-3.09 respectively). Arm paralysis was associated with poorer PSCI only at one year (OR=1.46; 95% CI=1.06-2.02). There was no interaction between limb paralysis and functional status. Aphasia was associated with PSCI at three years (OR=1.56; 95% CI=1.15-2.11); however, this association was confounded by interaction with OHS at baseline (p=0.018) (Suppl. tab.3). Subgroup analysis for ischaemic events (ischaemic strokes and TIA) confirmed age, female sex, stroke severity and diabetes as independently association with poorer cognitive performance at one and three years. Hypertension was also associated with cognitive impairment at three years. Leg paralysis remained associated with MMSE≤26 at both one and three years (OR=1.54; 95% CI=1.15-2.07; OR=1.82; 95% CI=1.16-2.85) (Tab.3), with no interaction with functional status at baseline. Aphasia was associated with cognitive impairment at one year (OR=1.35; 95% CI=1.06-1.72) and at three years (OR=1.78; 95% CI=1.26-2.53), but at three years there was evidence of interaction with functional status at baseline (p=0.028) (Supp. Tab.3). Neglect, hemianopia and sensory impairment were not associated with cognitive impairment at one and three years in both stroke groups.

Discussion

We investigated the associations between baseline stroke symptoms and post stroke cognitive impairment defined as MMSE≤26. As defined by this cut-off, in our cohort around one third of patients with stroke in the long term had cognitive impairment. Age, female sex, stroke severity, history of diabetes were associated with PSCI at one and three years and in all study groups. Among stroke symptoms, paralysis in the lower limb at baseline was consistently associated with PSCI.

Our results regarding age, female sex, diabetes are in keeping with previous studies[3,5] that demonstrated an increased risk of cognitive deficits after stroke. We found that hypertension was associated with PSCI after three years only in the ischemic stroke subgroup, this result is in line with the aforementioned Pendlebury and Rothwell metanalysis[5].

Interestingly, we found that leg paralysis at baseline appeared to be independently associated with cognitive impairment at both follow up time points. In addition, we observed a lack of interaction between leg paralysis and functional status at baseline. Gait problems may independently predict disability or death[12] and risk of both cognitive impairment and dementia[13,14]. In a population cohort study, hemiparetic gait has been associated both to vascular and non-vascular dementia[14]. A recent prospective study found that gait impairment after mild stroke increased the risk of developing cognitive decline after two years[15]. Assuming leg paralysis as a surrogate of gait dysfunction, our results are in keeping with such association.

In our study, aphasia increased the risk of cognitive impairment one year after ischaemic stroke/TIA, although associations at three years were confounded by interaction with functional status at baseline. We acknowledge that aphasia could negatively affect the assessment of cognitive status with MMSE, which relies on the language ability of the patient[16]. Since language is a cognitive domain, language deficits represent a subset of cognitive impairment, therefore this result needs to be interpreted with caution.

We acknowledge shortcomings that may have biased our results. First, the non-systematic assessment of cognitive function at follow up may have lead to an attrition bias. Although we found low mortality rates, our supplemental tables showed that selection likely favoured those with less neurological impairment. The higher rates of baseline symptoms such as paralysis or aphasia in patients without cognitive assessment at follow up seem to confirm that an attrition bias occurred. However, this fact may have underestimated rather than overestimate our results reducing the rate of patients with cognitive impairment[17]. Moreover, diagnosis of PSCI should be based on a comprehensive evaluation including a complete multi-domain neuropsychological battery. Use of a brief dementia screening tool, such as MMSE, is not a substitute for formal neuropsychological and clinical assessment. However, in the context of a multicentre clinical trial with many thousands of patients there is a necessary trade-off between diagnostic detail and feasibility. MMSE is a reasonable tool for detection of post stroke dementia and is commonly used in practice as well as in research.

Although a recent systematic review highlighted that MMSE is more specific than other screening tests for detection of cognitive impairment[11], the lack of sensitivity of the MMSE≤26 cut-off may underestimate the real prevalence of cognitive impairment[18,19]. Together with attrition bias, it seems likely that the prevalence of cognitive impairment after stroke is higher than we reported.

In conclusion, in our sample of patients with mild stroke, around 30-34% of patients experienced cognitive impairment between one and three years. We confirmed increasing age, female sex, stroke severity, history of diabetes as factors associated with PSCI. Among stroke features, leg paralysis may predict cognitive impairment in the long term follow up. Early detection of mobility impairment after stroke may help to identify patients at risk of cognitive impairment.

Disclosures: none.

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Appendix:

*VISTA-Prevention Steering Committee

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Table1. Baseline demographic and clinical characteristics of study population.

	Baseline **N=5453**	**1 Year** **N=2270**	**3 years** **N=1294**
Age, mean (±SD)	62.6 (±12.6)	64.1 (±11.9)	63.7 (±11.8)
Sex, male	3476 (64)	1515 (65)	848 (65)
OHS baseline, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)
Hypertension	3890 (71)	1664 (72)	925 (70)
Diabetes	1321 (24)	543 (23)	298 (22)
Ischaemic heart disease	928 (17)	397 (17)	201 (15)
Atrial fibrillation	420 (8)	179 (8)	98 (8)
Hypercholesterolemia	2299 (42)	1094 (47)	615 (47)
Smoker	1310 (24)	537 (23)	268 (20)
Depression	437 (8)	211 (9)	115 (9)
Arm paralysis	3753 (69)	1452 (63)	826 (63)
Leg paralysis	3310 (61)	1228 (53)	687 (52)
Aphasia/dysarthria	1438 (26)	541 (23)	261 (20)
Neglect	436 (8)	145 (6)	75 (6)
Sensory impairment	1780 (33)	732 (32)	462 (35)
Hemianopia	519 (10)	199 (9)	103 (8)

SD=standard deviation; OHS=Oxford Handicap Scale; IQR=Interquartile Range.

Table 2. Associations between baseline stroke symptoms and cognitive impairment (MMSE≤26) in all brain vascular events (ischaemic, TIA, haemorrhagic). Analysis adjusted for all the variables listed in the table.

	All stroke subtypes			
	One year CI		**Three years CI**	
	Unadjusted OR (95%CI)	**Adjusted OR (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR (95%CI)**
Age	1.03 (1.02-1.03)	**1.03 (1.02-1.04)**	1.04 (1.03-1.05)	**1.04 (1.03-1.06)**
Sex, female	1.53 (1.28-1.84)	**1.49 (1.22-1.80)**	1.95 (1.53-2.50)	**1.78 (1.37-2.31)**
OHS baseline	1.71 (1.53-1.91)	**1.38 (1.23-1.56)**	1.53 (1.32-1.78)	**1.30 (1.10-1.54)**
Hypertension	1.35 (1.11-1.65)	1.09 (0.88-1.35)	1.68 (1.27-2.22)	1.25 (0.93-1.68)
Diabetes	1.74 (1.43-2.13)	**1.57 (1.27-1.94)**	2.14 (1.63-2.82)	**1.86 (1.38-2.50)**
Arm paralysis	1.93 (1.60-2.33)	**1.46 (1.06-2.02)**	1.41 (1.09-1.81)	0.97 (0.60-1.59)
Leg paralysis	2.10 (1.75-2.51)	**1.62 (1.20-2.20)**	1.74 (1.37-2.23)	**1.95 (1.23-3.09)**
Aphasia	1.24 (1.01-1.51)	1.24 (0.96-1.60)	1.63 (1.23-2.17)	**1.67 (1.17-2.40)***
Neglect	1.13 (0.79-1.60)	-	0.97 (0.58-1.62)	-
Sensory impairment	0.90 (0.75-1.09)	-	0.82 (0.64-1.05)	-
Hemianopia	1.30 (0.96-1.76)	-	1.25 (0.81-1.91)	-

CI=Cognitive impairment; OR=odds ratio; CI=Confidence Interval.
*p for interaction with functional status=0.018.

Table 3. Associations between baseline stroke symptoms and cognitive impairment (MMSE≤26) in ischaemic events (ischaemic stroke and TIA). Analysis adjusted for all the variables listed in the table.

	Ischemic stroke/TIA			
	One year CI		**Three years CI**	
	Unadjusted OR (95%CI)	**Adjusted OR (95%CI)**	**Unadjusted OR (95%CI)**	**Adjusted OR (95%CI)**
Age	1.03 (1.02-1.04)	**1.03 (1.02-1.04)**	1.04 (1.03-1.06)	**1.04 (1.03-1.06)**
Sex, female	1.72 (1.40-2.12)	**1.57 (1.27-1.96)**	2.09 (1.59-2.77)	**1.86 (1.38-2.50)**
OHS baseline	1.49 (1.33-1.68)	**1.33 (1.18-1.51)**	1.40 (1.20-1.64)	**1.24 (1.04-1.48)**
Hypertension	1.47 (1.17-1.85)	1.24 (0.97-1.58)	1.89 (1.37-2.62)	**1.43 (1.01-2.03)**
Diabetes	1.68 (1.35-2.10)	**1.60 (1.27-2.02)**	2.32 (1.71-3.13)	**2.15 (1.56-2.97)**
Arm paralysis	1.80 (1.44-2.25)	1.30 (0.96-1.77)	1.37 (1.02-1.84)	0.81 (0.51-1.29)
Leg paralysis	1.95 (1.58-2.40)	**1.54 (1.15-2.07)**	1.71 (1.29-2.27)	**1.86 (1.19-2.92)**
Aphasia	1.40 (1.12-1.76)	**1.35 (1.06-1.72)**	1.79 (1.30-2.48)	**1.81 (1.28-2.57)***
Neglect	1.13 (0.78-1.65)	-	0.93 (0.54-1.61)	-
Sensory impairment	0.99 (0.81-1.23)	-	0.84 (0.63-1.11)	-
Hemianopia	1.27 (0.91-1.76)	-	1.36 (0.86-2.16)	-

CI=Cognitive impairment; OR=odds ratio; CI=Confidence Interval.

*p for interaction with functional status=0.028.