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ORIGINAL ARTICLES

Incidence and risk factors of delirium in patients with acute ischaemic stroke

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Abstract

Background & Objectives: The reported incidence of post-stroke delirium varies substantially in current medical literature. The impact of delirium on mortality and morbidity is significant and there is need for sustained research on the topic. We aimed to determine the incidence, risk factors and outcome of delirium in acute ischaemic stroke. *Methods:* We conducted a cross-sectional observational study on consecutive patients with ischaemic stroke. The Confusion Assessment Method was used to diagnose delirium within seven days of stroke onset. *Results:* Two hundred and eighty patients were recruited (mean age 63.6 years) and 36 (12.9%) developed delirium. After adjustments for covariates, age >65 years (odds ratio, OR 5.2; 95% confidence interval 1.6-17.5); pre-existing dementia (6.5; 1.1-38.2); TACI (7.2; 1.5-35); and a National Institute of Health Stroke Scale of ≥10 (6.8; 1.7-26.4), were independently associated with a risk of developing delirium. Lacunar infarcts were not associated with delirium (0.07; 0.03-0.16). The majority of patients with delirium were cared for in a dedicated stroke unit but this proportion was not significant compared to those without delirium (69.4% vs 58.2%, p=0.20). Delirious patients had significantly higher in-patient mortality (8.3% vs 0%, p=0.002) and longer length of hospital stay (6.94 vs 3.98 days, p< 0.001).
Conclusions: One in 8 patients with ischaemic stroke in our centre developed delirium. Older age, pre-existing dementia and severe stroke were independent predictors of delirium. Patients with lacunar infarcts did not develop delirium as often as those with other stroke types. Delirium significantly increased in-patient mortality and length of hospital stay.

Keywords: Delirium, acute confusional state, ischaemic stroke, risk factors, incidence

INTRODUCTION

Delirium, an important but under-recognised complication of stroke, is characterized by decreased attention and awareness, with changes in cognition. It develops over a short period of time and typically fluctuates.[1-3] Delirium is more common in patients with stroke (13%–48%) compared to those admitted with general medical conditions (10-25%).[4,5] Previous research has demonstrated that a higher risk of delirium in stroke is associated with older age, pre-existing dementia, stroke severity, left sided infarction, total anterior circulation stroke, cardio-embolic stroke, hemineglect and visual impairment.[6] Post-stroke delirium results in higher mortality, prolonged hospital stay and increased institutionalisation rates.[6-8]

Delirium, in general, may be triggered by infection, seizures, metabolic disorders, falls, medication, urinary retention, constipation and pain.[9] Several mechanisms have been postulated in the pathophysiology of delirium, most commonly the neurotransmitter imbalance of cholinergic deficiency and dopamine excess observed in

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neuroinflammation.[10]

All previous studies of delirium in stroke have included patients with ischaemic and haemorrhagic stroke, and most have only included patients admitted to stroke units.[11] There is no dedicated research on the incidence of delirium in ischaemic stroke, as a distinct entity. We aimed to determine the incidence and risk factors of delirium in a cohort of ischaemic stroke within the first week of stroke. In secondary analyses, we assessed the effect of stroke unit care on the incidence of delirium and the effect of delirium on patient outcome.

METHODS

We conducted a cross-sectional, observational study of patients admitted to our centre, a tertiary teaching hospital with a comprehensive stroke service. Data collection was performed over an 18-month period (June 2015-December 2016). Consecutive patients with acute ischaemic stroke and aged ≥ 18 years, admitted to the stroke care unit (SCU) or general medical wards were screened. Inclusion criteria included a clinical diagnosis of ischaemic stroke on admission and duration of stroke of ≤ 7 days at the time of recruitment. We excluded patients with haemorrhagic stroke, a Glasgow Coma Scale score (GCS) of < 8 or requiring mechanical ventilation. All participants or legal representatives provided written informed consent. The study was approved by the institution's research and ethics committee (FF2015-124).

We recorded baseline demographic data and comorbidities (diabetes mellitus, atrial fibrillation, hypertension, ischaemic heart disease, dyslipidaemia, previous stroke or transient ischaemic attack and pre-existing dementia) to identify possible risk factors of delirium. Participants were considered to have pre-existing dementia if prior diagnosis was made by a specialist and based on family report. We classified stroke using the Oxfordshire Community Stroke Project (OCSP) classification[12], based on neuroimaging (CT scan and MRI) and clinical features. Information was obtained from the patients or relatives and review of the hospital's electronic database.

All participants were assessed within seven days of stroke, by a single assessor (BHN), who was trained in use of the Confusion Assessment Method (CAM). The CAM was used to screen for delirium, performed once within the seven-day period. The CAM consists of four features: 1) acute and fluctuating course; 2) inattention; 3) disorganised thinking and 4) altered level of consciousness. Delirium is considered to be present if items 1 and 2 and either one of items 3 or 4 are present.[5] The CAM can be used to distinguish delirium from other types of cognitive impairment. It demonstrates a sensitivity of 94%, and specificity of 89%.[13] The final diagnosis of delirium was confirmed by the treating neurologist. Stroke severity was evaluated using the National Institute of Health Stroke Scale (NIHSS) at day 1 after admission and functional status at time of discharge was evaluated using the modified Rankin Scale (mRS).

The primary outcome was a diagnosis of delirium based on the CAM within 7 days of onset of stroke. Secondary outcomes include in-patient mortality, length of hospital stay and institutionalisation rate.

Sample size was calculated using the formula $n = (Z_{1-\alpha})^2 [P (1-P) / D^2]$[14] with prevalence, P estimated to be 25% and precision (D) of 0.05. The target sample size was determined to be 288 patients.

Statistical analyses were performed using SPSS, version 23. The Student t-test and Mann Whitney U tests were used to compare differences between patients with and without delirium for continuous variables and the Pearson Chi-square test was used to analyse categorical variables. Univariate followed by multivariate binary logistic regression analyses were used to determine the independent risk factors associated with post-stroke delirium. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

We recruited 280 participants. There were 186 (66.4%) males and the mean age of our sample was 63.6 ± 13.7 years. Co-morbid illness included hypertension (75.7%), diabetes mellitus (42.9%), dyslipidaemia (35.7%), previous stroke (22.5%), ischaemic heart disease (17.1%) and atrial fibrillation (5.7%).

Lacunar infarction (LACI) was the commonest stroke type (n=198, 70.7%) followed by partial anterior circulation infarction (PACI; n=30, 10.7%), total anterior circulation infarction (TACI; n=28, 10%) and posterior circulation infarction (POCI; n=24, 8.6%). The characteristics and risk factors of the patients with and without delirium are shown in Table 1.

Table 1: Baseline clinical characteristics of stroke patients with and without delirium

Characteristics	Total (n=280)	Delirium (n=36)	No delirium (n=244)	p value
Age (years)	63.6 (13.7)	71.0 (12.4)	62.5 (13.6)	< 0.001
Sex (male)	186 (66.4)	21 (58.3)	165 (67.6)	0.27
Recent alcohol intake*	2 (0.7)	1 (2.8)	1 (0.4)	0.12
Pre-existing dementia	8 (2.9)	4 (11.1)	4 (1.6)	0.001
Prior stroke	63 (22.5)	9 (25%)	54 (22.1)	0.70
Atrial fibrillation	39 (13.9)	8 (22.2)	31 (12.7)	0.12
Ischaemic heart disease	48 (17.1)	8 (22.2)	40 (16.4)	0.39
Diabetes mellitus	120 (42.9)	12 (33.3)	108 (44.3)	0.22
Hypertension	212 (75.7)	28 (77.7)	184 (75.4)	0.76
Dyslipidaemia	100 (35.7)	14 (38.9)	86 (35.2)	0.67
Multiple comorbidities†	176 (62.9)	25 (69.4)	151 (61.9)	0.38
Polypharmacy (≥2)	272 (97.1)	35 (97.2)	237 (97.1)	0.98
Care setting-SCU	167 (59.6)	25 (69.4)	142 (58.2)	0.20
NIHSS (/42)	4 [2, 9]	17.5 [9.3, 24.8]	3 [1,7]	< 0.001
OCSP				< 0.001
TACI	28 (10)	19 (52.8)	9 (3.7)	
PACI	30 (10.7)	6 (16.7)	24 (9.8)	
POCI	24 (8.6)	4 (11.1)	20 (8.2)	
LACI	198 (70.7)	7 (19.4)	191 (78.3)	

Data are number (%) or mean (standard deviation) or median [interquartile range]. Data was analysed using Chi-square test for categorical and Mann-Whitney U and t-test for continuous variables. *Alcohol intake in the 7 days prior to onset of stroke. †Two or more comorbidities. SCU= stroke care unit; NIHSS=National Institute of Health Stroke Scale; OCSP=Oxfordshire Community Stroke Project; TACI= total anterior circulation infarction; PACI= partial anterior circulation infarction; POCI= posterior circulation infarction; LACI= lacunar infarction

Incidence, risk factor and outcome of delirium

Post-stroke delirium was detected in 36 participants (12.9%). Patients who developed delirium were older compared to those who did not (mean age of 71 versus 62.5 years), had a more severe stroke, as shown by a higher NIHSS score and higher proportion with total anterior circulation infarction (Table 1). There were no statistically significant differences in the incidence of delirium comparing sex, the presence of risk factors, previous stroke and ischaemic heart disease.

Patients with delirium were more likely to have middle cerebral artery (MCA) infarction (Table 2). Conversely, delirium was less likely in patients with lacunar infarction. Table 2 illustrates the laboratory and neuroimaging findings of patients with and without delirium.

Post-stroke complications were present in 35 patients (12.5%, Table 3) including pneumonia (n=24, 8.6%), fever (22, 7.9%), hypoxia (9, 3.2%), urinary tract infection (3, 1.1%), seizures (2, 0.7%) and pulmonary embolism (1, 0.4%). Delirium is significantly more common in patients with pneumonia, fever, hypoxia or seizures.

Based on univariate analysis, total anterior circulation infarction (TACI), middle cerebral artery (MCA) infarction, pre-existing dementia, higher NIHSS and older age (>65 years) were associated with the occurrence of post-stroke delirium (table 4). Multivariate logistic regression revealed that factors independently associated with post-stroke delirium were age >65 years (odds ratio, OR 5.2; 95% confidence interval 1.6-17.5), pre-existing dementia (6.5; 1.1-38.2), TACI (7.2; 1.5-35) and NIHSS of ≥10 (6.8; 1.7-26.4).

Table 2: Laboratory test and neuroimaging of patients with and without delirium

Variables	Total (n=280)	Delirium (n=36)	No delirium (n=244)	p value
Elevated white cell count*	48 (17.1)	8 (22.2)	40 (16.4)	0.39
Sodium (mmol/L)	137.5 (3.2)	137.7 (4.9)	137.5 (2.8)	0.28
Potassium (mmol/L)	4.0 (0.5)	3.9 (0.5)	4.0 (0.5)	0.53
Calcium (mmol/L)	2.37 (0.12)	2.38 (0.10)	2.37 (0.12)	0.32
Urea (mmol/L)	6.0 [4.0, 6.9]	6.0 [4.8, 7.9]	5.0 [3.9, 6.8]	0.017
Creatinine (μmol/L)	83.5 [71, 104.5]	80.6 [63.9,103.3]	83.6 [72.4, 104.6]	0.10
Estimated GFR (mL/min/1.73m^2)†				0.62
≥90	88 (31.4)	11 (30.6)	77 (31.6)	
60-89	121 (43.2)	14 (38.9)	107 (43.9)	
30-59	55 (19.6)	10 (27.8)	45 (18.4)	
15-29	9 (3.2)	1 (2.8)	8 (3.3)	
<15	7 (2.5)	0 (0)	7 (2.9)	
Neuroimaging-infarction¶				<0.001
MCA	46 (16.4)	24 (66.7)	22 (9.0)	
ACA	10 (3.6)	0 (0)	10 (4.1)	
PCA	14 (5)	2 (5.6)	12 (4.9)	
Brainstem/ cerebellar	13 (4.6)	2 (5.6)	11 (4.5)	
Lacunar	197 (70.4)	8 (22.2)	189 (77.5)	
Left hemisphere¶	135 (48.2)	23 (63.9)	112 (45.9)	0.047
Leukoaraiosis¶	76 (27.1)	6 (16.7)	70 (28.7)	0.13

Data are number (%) or mean (standard deviation) or median [interquartile range]. * White cell counts of ≥12 X10^9/L. †MDRD (modification of diet in renal disease) formula. ¶Computed tomography scans were available in all patients and magnetic resonance imaging available in 11 (4%) patients. GFR=glomerular filtration rate; MCA=middle cerebral infarction; ACA=anterior cerebral artery; PCA=posterior cerebral artery

Table 3: Comparison of medical complications in patients with and without delirium

Complications	Total	Delirium	No delirium	p value
Fever	22 (7.9)	9 (25)	13 (5.3)	<0.001
Pneumonia	23 (8.2)	14 (38.9)	9 (3.7)	<0.001
Hypoxia	9 (3.2)	5 (13.9)	4 (1.6)	<0.001
UTI	3 (1.1)	1 (2.8)	2 (0.8)	0.29
DVT/PE	1 (0.4)	0 (0)	1 (0.4)	0.70
Seizure	2 (0.7)	2 (5.6)	0 (0)	<0.001

Data are numbers (%). Chi-square test was used for analysis. DVT=deep vein thrombosis; PE=pulmonary embolism; UTI=urinary tract infection

Table 4: Univariate and multivariate logistic regression analysis of risk factors associated with post-stroke delirium

Characteristic	Univariate Unadjusted OR (95% CI)	p value	Multivariate Adjusted OR (95% CI)	p value
Age >65 years	4.1 (1.9-9.1)	0.001	5.2 (1.6-17.5)	0.007
Pre-existing dementia	7.5 (1.8-31.5)	0.006	6.5 (1.1-38.2)	0.037
TACI	29.2 (11.5-74.2)	<0.001	7.2 (1.5-35)	0.014
MCA infarction	20.2 (8.9-45.9)	<0.001	4.2 (1.0-17.9)	0.055
NIHSS		<0.001		0.019
0-4	Reference	-	Reference	-
5-9	3.8 (1.0-14.6)	0.054	2.5 (0.6-10.9)	0.22
≥10	30.3 (10.0-92.1)	<0.001	6.8 (1.7-26.4)	0.006

* Model adjusted for age, sex and admission to stroke unit. No significant multicollinearity in final model (variance inflation factor <3). Model fitness checked with Hosmer-Lemeshow goodness of fit test (p=0.75). NIHSS=National Institute of Health Stroke Scale, mRS= modified Rankin Scale, TACI= total anterior circulation infarction; OR=odds ratio; 95% CI=95% confidence interval.

Tables 4 provide a summary of the univariate and multivariate analysis of patients with and without delirium.

Approximately 60% of our stroke patients were treated in a stroke care unit (SCU) and 25 of them developed delirium. The proportion of patients with delirium was higher amongst those cared for in the SCU (69.4%) compared to those in the general wards. Although more patients with delirium were nursed in the SCU, the proportion of SCU patients with delirium compared to those without (58.2%) was not significant (p=0.20).

Delirious patients had significant in-patient mortality (8.3% *vs* 0%, p<0.001) and prolonged hospital stays. The mean duration of hospital stay in patients with delirium was 6.94 ± 3.79 days *vs* 3.98 ± 3.86 days in those without delirium (Table 5). Only 3 patients (1.1%) were discharged to a nursing home while the rest were discharged home.

DISCUSSION

The frequency of post-stroke delirium in our study is 12.9%, falling within the lower range of previously reported incidence (13% to 48%).[3] Our study is the first to assess the incidence of delirium in ischemic stroke alone and has implications for post-stroke care. The lower incidence of delirium in our cohort may be attributed to several factors. Firstly, we excluded patients with GCS of ≤8, and by extension of that exclusion, we did not recruit stroke patients admitted directly to the general intensive care unit. Secondly, we excluded patients with intracerebral haemorrhage. Thirdly, the majority of our cohort had lacunar stroke which is not typically associated with post-stroke delirium.[15] The high proportion of lacunar infarction in our population has been previously published.[16] Fourthly, our cohort of patients is younger to those in similar studies.[11]

Exclusion of patients with severe stroke requiring intubation and ICU care was by design. We excluded haemorrhagic stroke as these patients are a unique group and warrant separate study, especially because the incidence of delirium is higher in this group.[17] Furthermore, a proportion of patients with haemorrhagic stroke have underlying amyloid angiopathy suggesting the presence of

Table 5: Outcomes of patients with and without delirium

Outcomes	Total	Delirium	No delirium	OR (95% CI)	p-value
Inpatient mortality	3 (1.1%)	3 (8.3%)	0 (0%)	-	0.002*
Length of Stay (days)	4.36 (3.97)	6.94 (3.79)	3.98 (3.86)	1.14 (1.06 – 1.23)	< 0.001†

Data is presented as n (%) or mean (standard deviation). *Chi-Square test; †Binary logistic regression

pre-existing dementia, a recognised risk factor for delirium.[18]

Previous studies have identified older age, pre-existing dementia, stroke severity, left sided-stroke, total anterior and posterior circulation stroke, and the presence of neglect or visual impairment as risk factors for delirium.[6] In our univariate analyses, TACI, middle cerebral artery infarction, pre-existing dementia, high NIHSS and mRS scores, and older age were associated with the development of post-stroke delirium. Following multivariate analyses TACI, high NIHSS score (>10), older age and pre-existing dementia remained significant.

We have demonstrated that TACI independently predicts delirium. We were then able to ascertain, that within this group, only MCA stroke was associated with a significant risk of developing delirium but missed statistical significance on multivariate analysis (p=0.055). No patients with ACA infarction developed delirium but this cohort of patients was small (n=10). As a group, TACI remained a significant risk for developing delirium on multivariate analysis, and this association is in keeping with previous research.[19] TACI tend to cause larger stroke, with cortical involvement and impaired higher functions, which may be responsible for the higher incidence of delirium in these patients.

In our cohort, a significant number of patients, approximately 70%, had lacunar infarctions but this subgroup of patients was not at increased risk of delirium. Only 7 patients with lacunar infarct developed delirium. Our findings suggest that sub-cortical infarctions do not increase the risk of delirium and supports the argument that involvement of the cerebral cortex is an important determinant of delirium risk. Previous studies have demonstrated that lacunar strokes are less likely to cause delirium. However, the proportion of lacunar infarcts in our cohort is the largest and the number of patients developing delirium is significantly low. Moreover, the previous studies have not reliably and consistently made the distinction between various ischemic stroke types.

In keeping with the argument the stroke area and size influence the development of delirium, we also demonstrated that stroke severity was an independent predictor of delirium, similar to previous reports.[15] One plausible explanation is, the greater size of infarction the greater the disability and its associated medical complications. Furthermore, severe strokes reflect larger infarcts with a higher risk of cortical involvement, more neuro-inflammation and possibly a more marked disturbance of neurotransmission.

Advancing age is a known predisposing factor for delirium, generally, and in stroke patients specifically.[11] This may be explained by the higher risk of dementia, age-related loss of cholinergic reserve and loss of acetylcholine in the nucleus basalis of Meynert. We found that delirium was more common amongst older patients and our findings are in keeping with several previous studies.[2,7,8,15,20-22]

Pre-existing cognitive impairment is also a recognised and important risk of developing delirium in the general population.[23] Henon *et al*. and Gustafson *et al*. have reported pre-existing cognitive impairment as an important risk factor for post-stroke delirium.[7,20] Existing cognitive impairment suggests a lower level of cognitive reserve and this may explain the increased risk of delirium.

The majority of patients who developed delirium were cared for in the SCU. In our centre, patients with more severe stroke and those who have been thrombolysed are given priority for admission to SCU when there is shortage of beds. Therefore, it is more likely that the risk of delirium in these patients is a reflection of the severity of their stroke, rather than whether they were cared for in an SCU or general medical ward. Admission to a stroke unit is recommended for all stroke patients, and is one of the few care strategies proven to improve outcome.[24] The admission criteria to the SCU that we have adopted are not a disregard for current evidence. Rather, it is based on a policy of judicious utilization of limited resources true of most lower and middle-income economies.

In our study, pneumonia was an important trigger for delirium, concurring with previous studies.[7,10,25] Systemic infections are associated with increased secretion of inflammatory mediators and microglial activation, which subsequently produce cytotoxic substances, weaken astrocytic tight junctions and affect neuronal function.[26] This may explain the role of systemic infections in the development of acute confusional states. Complications such as urinary tract infections and pulmonary embolism may have triggered delirium as well, though the association was not significant due to small number of patients affected.

The mean duration of hospital stay was longer in patients with delirium (6.94 days versus 3.98 days) and delirious patients had significant in-patient mortality (3.8% versus 0%). Our findings

are consistent with previous reports and a recent meta-analysis which showed increased mortality after delirium.[6,19,27,28] We were unable to accurately determine if delirium impacted on discharge destination as the majority of our patients were discharged home regardless of the level of dependence. This reflects local practice where very few patients are transferred to institutional care facilities due to societal norms and prohibitive cost.

The strengths of our study are that we included only ischaemic stroke patients and therefore, the estimation of risk attributed to stroke location, type and severity is more accurate. Previous studies did not make the distinction between ischaemic and haemorrhagic stroke. Haemorrhagic strokes have distinctively different mechanisms of brain injury from ischaemic stroke. Cerebral complications such as haematoma expansion in intracerebral haemorrhage and cerebral vasospasms in subarachnoid haemorrhage may lead to higher rates of neurological deterioration and delirium. We were also able to recruit a relatively large cohort of patients. The evaluation of delirium was performed by a single assessor, ensuring consistency. Our patients were admitted to either the stroke unit or general medical ward. This reflects the real-world scenario in many parts of the world, where not all patients benefit from stroke unit admission, due to a limitation of resources. Lastly, the majority of studies on post-stroke delirium were carried out in Western countries.[11,27] This study provides a valuable addition to the literature on post-stroke delirium in an Asian population.

Our assessment is based on a single-centre prospective observational study, which limits the generalizability of our data. The risk factors we have identified are an association and need to be studied in a larger sample of patients. We assessed patients for delirium repeatedly within 7 days of stroke, due to constraints of cost and time, and do not have longer term outcomes. Some of our estimates are based on low incidence levels and this may reduce reliability of our analyses. Similar analyses in a larger sample or better utilisation of pooled data will provide us with more reliable estimates. In patients with no previous formal diagnosis of dementia, we did not screen for cognitive impairment. Therefore, we might have underestimated those with pre-existing undiagnosed dementia.

Delirium occurred in one in 8 patients in our cohort of purely ischaemic stroke. We identified that TACI, stroke severity, older age and pre-existing dementia were independently associated with delirium. Pneumonia was a significant trigger of delirium and patients with delirium had higher inpatient mortality and prolonged hospitalization.

Based on our findings, and data from previous published research, suggest that the risk of delirium can be predicted. There is at least one validated delirium prediction score specifically for use in stroke.[29] Early stratification of patients at risk may prevent prolonged hospitalization, reduce complications and improve clinical outcomes. The long-term impact of delirium on cognitive function, functional outcome and long-term mortality needs to be studied. We recommend that screening for delirium be included as part of standard stroke assessment.

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DISCLOSURE

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