Title: Occurrence rate of delirium in acute stroke settings – systematic review and meta-analysis

Running Title: Delirium in acute stroke

Word Count:4818

Abstract:250

Keywords:delirium,stroke,systematic review

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Tables:3

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Background and purpose: Delirium is associated with increased mortality, length of stay and poor functional outcome following critical illness. The epidemiology of delirium in stroke is poorly described. We sought to collate evidence around occurrence (incidence and/or prevalence) of delirium in acute stroke.

Methods: We searched multiple, cross-disciplinary electronic databases using a pre-specified search strategy; complemented by hand searching. Eligible studies described delirium in acute (first six weeks) stroke. We compared delirium occurrence using random effects models to describe summary estimates. We assessed risk of bias using the Newcastle-Ottawa tool, incorporating this in sensitivity analyses. We performed subgroup analyses for:delirium diagnostic method (confusion assessment method scoring [CAM]; clinical diagnosis; other); duration and timing of delirium assessment (greater or less than one week) and performed meta-regression based on year of publication.

Results: Of 8,822 titles, we included 32 papers (6,718 participants) in the quantitative analysis. Summary estimate for occurrence of delirium was 25% (95%CI:20%-30%, moderate quality evidence). Limiting to studies at low risk of bias (22 studies, 4,422 participants) the occurrence rate was 23% (95%CI:17%-28%). Subgroup summary estimates suggest that delirium occurrence may vary with assessment method:CAM:21% (95%CI:16%-27%); clinical diagnosis:27% (95%CI:19%-38%); other:32% (95%CI:22%-43%) but not with duration and timing of assessment. Meta-regression suggested decline in occurrence of delirium comparing historical to more recent studies (slope-0.03(SE:0.004) $p<0.0001$).

Conclusions: Delirium is common, affecting one in four acute stroke patients. Reported rates of delirium may be dependent on assessment method. Our estimate of delirium occurrence could be used for audit, to plan intervention studies and inform clinical practice.

PROSPERO registration number:CRD42015029251

Introduction

Delirium is a serious neuropsychiatric complication of critical illness. Delirium adversely affects mortality and functional outcomes in many healthcare settings.[1] There are limited published data on delirium in stroke but available evidence suggests a similar pattern of higher mortality and poorer outcome.[2] Evidence based intervention for delirium is described[3,] and recent guidance emphasises the importance of routinely observing and testing for delirium in high risk groups such as unscheduled older adult hospital admissions.[4] International stroke guidelines do not explicitly mention delirium, but screening for delirium in acute stroke settings is increasingly performed.[5]

Estimates from studies describing delirium rates following stroke have varied considerably.[6,7] Methodological factors may have influenced the delirium rates described.[8] Some studies have tested for delirium over a defined time period[9] while others have only described point prevalence.[10] Equally the assessment methods used to detect delirium[11] have varied across studies.[12-14] It is also possible that delirium rates may have changed over time. Delirium is said to be a marker of quality of care[15] and in the context of improving stroke care in the last decade, temporal change in rates of delirium seem plausible. Active screening for delirium may have led to increased detection rate or better care processes may have led to reduced rates. Any attempt to review delirium epidemiology needs to address these points.

A contemporary synthesis of the available literature that offers robust estimates of rates of delirium in stroke could be useful for clinical practice, policy and research. The aim of this review was to collate the available evidence to allow a description of the occurrence (the combination of incident (develops after admission) and prevalent (present on admission)) delirium in patients hospitalised with acute stroke. Our secondary aims were to look at the effect of method of delirium assessment, timing and duration of assessment and temporal change.

Methods

The data that support these systematic review findings are presented in the main manuscript and supplementary materials, any other study level data not included in these materials are available from the corresponding author upon reasonable request.

We followed Preferred Reporting in Systematic Review and Meta-Analysis (PRISMA) guidance for the conduct and reporting of this review. We created a protocol, available through the PROSPERO registry (registration number:CRD4201502951,submitted 13/11/2015,http://www.crd.york.ac.uk/PROSPERO/)

Each aspect of the review was performed by at least two reviewers trained in systematic review methodology (RS,GW,EE) with access to a third arbitrator (TQ) as required.

Search strategy: Electronic database searching used a sensitive search strategy, employing validated search filters for concepts of 'stroke' and 'delirium' (Supplementary Methods I) combined with the Boolean operator "and". We searched multiple, cross-disciplinary electronic databases:MEDLINE (OVID),EMBASE (OVID),PsycINFO (EBSCO),psycARTICLES (EBSCO),CINAHL (EBSCO),Alois (Cochrane), from inception to June 2018.

References from reviews and other relevant studies were assessed for additional titles. We hand searched relevant high impact journals:Stroke (American Heart Association); International Journal of Stroke, (World Stroke Organisation) and Age and Aging (British Geriatrics Society) for relevant articles published between January 2010 and June 2018. Process continued until no new titles were found.

If relevant abstracts were discovered but the paper was not available the author was contacted regarding publication status. Where relevant data were not available in the published manuscript we also contacted authors. We translated foreign language papers.

Population:"Acute" stroke was defined as the period from ictus to six weeks post event. The definition of stroke was based on World Health Organisation definition.[16] We included studies where TIA or minor stroke were admitted. Where studies included a mixed population of stroke and subarachnoid haemorrhage or traumatic brain injury, we excluded those studies where these groups comprised more than 15% of the total population, as their psychological sequela may differ from other stroke syndromes.

Inclusion/exclusion: We screened titles and abstracts for relevance on the basis of the following inclusion and exclusion criteria. Studies describing human stroke survivors in any languages were considered. Cross-sectional, prospective and other cohort study designs were eligible. We excluded case studies with too few patients to gain reliable conclusions (<20 patients with stroke) and studies of delirium tremens. Case-control studies and randomised control trials were excluded as they would not give representative population data. Although we searched 'grey literature', we restricted inclusion to studies published in peer reviewed journals.

Data extraction: We extracted data from eligible papers to a pre-specified and piloted proforma, based on the Cochrane data extraction tool.[17] We extracted an estimate of delirium rate, corresponding variance and details relevant to subgroup analyses. We recorded inclusion/exclusion criteria of the studies and whether patients were excluded

on the basis of stroke impairments or pre-existing psychiatric diagnosis, including dementia.

We assessed internal and external validity using the Newcastle Ottawa assessment for cross-sectional studies.[18] The tool was modified for this study by making the "exposure" stroke and the "outcome" delirium. The modified tool was piloted on two papers and refined as necessary.(Supplementary Methods II) We assessed each domain and made a judgement on risk of bias at study level.

We made an assessment of overall strength of evidence based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework, modified to be suitable for an observational epidemiology question.[19] We assessed risk of bias; consistency of results (heterogeneity); directness (applicability of included studies to research question); precision (based on confidence intervals of summary estimate) and publication bias (funnel plot).

Analyses: As a validation of our search strategy, we compared included studies from our initial search to a list of three preselected papers relevant to the topic, to ensure these papers were returned and selected.[8,20,21]

We created a forest plot of all estimates and 95% confidence intervals. Given the likely heterogeneity in the included datasets, we favoured random effects models for summary estimates of delirium occurrence. We assessed for heterogeneity using a visual assessment of forest plots and a quantitative assessment (Higgin's I^2).

We conducted sensitivity analyses based on quality assessment, limiting analysis to those studies judged to be at low risk of bias in all areas or where only one area was uncertain. We performed subgroup analyses based on method of assessment, period and duration of assessment. For assessment method we categorised as 'clinical diagnosis' (using

recognised clinical classification such as Diagnostic and Statistics Manual [DSM])[22], 'Confusion Assessment Method [CAM]'[14] (the most widely used delirium assessment tool) and 'other'. We categorised period of assessment as timing of assessment in relation to stroke (patients tested at <1 week or >1week); duration of assessment compared single assessment to multiple assessments. To assess for temporal change in delirium occurrence, we inspected the forest plot re-arranged in chronological order performed meta-regression of log delirium rate against year of study. We assessed publication bias using a funnel plot. All quantitative analyses were performed using Comprehensive Meta-Analysis (version 2.2,USA).

Results

With duplicates removed we assessed 8,822 titles. Of 132 full text papers assessed, 32[6,7,9,10,12-14,21-46] were included in quantitative analysis (6718 patients). The review included cohorts from 19 different countries. Only one eligible article was not published in English (Russian)[29] and study author assisted with data extraction in English. Six relevant abstracts were not included as authors reported that full papers had not been written and there were no immediate plans to do this.(Figure 1) Our search strategy was proven valid as our three pre-selected papers were returned on initial search.

Across 32 included studies, there was variation in the included patients (Tables 1-2, Supplementary Table I) and variation in delirium occurrence:range 6.7%[6] to 61%.[32](Figure 2a,b) There was substantial statistical heterogeneity in the results, I^2 value:93.6%. The summary value of delirium occurrence was 25% (95%CI:20%-30%). (For comparison, the fixed effects estimate was 24% (95%CI:23%-25%).

We judged 22 studies (n=4422 participants) to have low risk of bias. The main reason for scoring high or uncertain risk of bias was around selection of the population (13/32 papers [41%]), with studies excluding those patients likely to be at highest risk of delirium, for

example pre-existing dementia or severe stroke.(Table 3) On sensitivity analysis limited to studies considered low risk of bias, summary value for delirium occurrence was 23% (95%CI:18%-28%).(Supplementary Figure I)

There were 26 different tests used in the assessment of delirium or cognition across the 32 papers. On subgroup analysis by method assessment, validated clinical diagnosis [DSM] (n=11 studies; n=1827participants) gave a summary estimate of 27% (95%CI:19%-38%); CAM (n=15 studies; n=3702participants) gave a summary estimate of 21% (95%CI:16%-27%), other diagnosis (n=6 studies; n=634participants) gave a summary value of 32% (95%CI:22%-43%).(Supplementary Figure II)

On subgroup analysis describing period of assessment, testing for <1 week (n=15 studies; n=2592 participants) gave a summary delirium occurrence of 24% (95%CI:18%-31%) while testing for>1 week (n=16 studies; n=3887 participants) gave a summary estimate of 24% (95%CI:18%-31%).(Supplementary Figure III) On exploratory subgroup analysis of studies only assessing participants at one time-point (n=16 studies; n=2594participants) summary value for delirium was 24%(95%CI:19%-31%) while studies conducting repeat (>1) assessments (n=15 studies; n=3052participants) had a summary value of 26%(95%CI:20%-33%).(Supplementary Figure IV)

Meta-regression showed an inverse relationship between year of study and delirium occurrence (slope-0.03(SE:0.004) p<0.0001).(Figure 3) The more recent studies reported lower delirium occurrence, for example 1987 delirium occurrence:0.61 (95%CI:0.45-0.75, 1 paper); 2017 delirium occurrence:0.16 (95%CI:0.13-0.18, 4 papers).

Our funnel plot analysis suggested no substantial publication bias.(Supplementary Figure V) The overall assessment of quality of evidence was graded as moderate. We deducted points for inconsistency in individual study estimates and due to uncertain risk of bias we chose the moderate descriptor.(Figure 1)

Discussion

Our systematic review suggests high rates of delirium in stroke; with around one in four having delirium in the acute period. Although there were issues with heterogeneity and risk of bias, our estimates remained reasonably robust in a series of sensitivity and subgroup analyses.

To put our results in context, a previous review of delirium post stroke, published in 2010, gave a similar estimate of incident events (26%, range:2-66%).[8] However, the majority of papers included in our review (23 papers [72%]) were published since 2010, demonstrating the growing interest in this area. The between study heterogeneity will in part relate to case-mix and we note differing ages and comorbidities of included populations. Recent estimates of delirium in medical inpatients, excluding stroke, suggest occurrence of 20% reaching greater than 40% in older adults.[47] In a review of delirium in critical care delirium occurrence ranged from 45-87%.[48] Stroke is an emergency condition typically seen in older adults and so, one may have expected delirium occurrence to be closer to the 40% reported in these populations.

Various approaches were used to assess for delirium. If we consider clinical diagnosis using DSM or similar as 'gold standard', our results suggest that assessment with the CAM screening tool may under-estimate delirium, while use of bespoke and non-validated tools may over estimate, albeit there was some uncertainty and confidence intervals overlapped. Various assessments of cognition were used, many of which are not recommended in delirium assessment guidance.[5] It is notable that the 'outliers' in our analyses, on the whole, used non-validated approaches to delirium assessment.

Our subgroup analysis describing period of assessment suggested no difference when comparing longer and shorter assessment. Intuitively, assessing over a longer period should give higher occurrence as there is a longer time for incident delirium secondary to

complications of stroke. Our data are consistent with previous studies where majority delirium was detected on the first day of admission and the remainder appeared within the next 5 days.[14] This 'front loading' of delirium could be due to the patient conditions tending to be worse on admission and then improving with specialist stroke unit care. The same pattern is seen with delirium in acute medical admissions[49] and highlights that screening and preventive interventions need delivered as soon as possible.

Our meta-regression confirms a temporal trend towards decreasing delirium incidence over time. There are many potential reasons for this encouraging result and the explanation is likely to be multifactorial. One plausible reason is that the specialist multidisciplinary care offered in stroke units is similar to the multicomponent interventions proven to reduce delirium incidence in older adult inpatients.[15] This may also explain why our rates of delirium occurrence, while high, are lower than seen in other critical care settings.

Through our comprehensive search strategy, stringent inclusion/exclusion criteria, assessment of risk of bias and pre-specified subgroup analyses we feel we offer a valid summary of the published literature on delirium in stroke. There are caveats to the interpretation and application of GRADE and funnel plots in observational epidemiology and as with any systematic review, conclusions are limited by the validity of the studies available in the published literature.

There are reasons to suspect that the 'real world' occurrence of delirium may be higher than our estimates. This is reflected in our GRADE assessment of moderate quality. We note that many of the studies in our review excluded patients with pre-stroke dementia, a factor which is common and associated with incident delirium. Other studies excluded patients with aphasia, severe illness or those unable to be tested, all of which are likely to systematically under-estimate delirium. We recognise the difficulty in performing

neuropsychological assessment in those with such impairments, but assessment for delirium is possible with sufficient time and training.

We have described a high occurrence of delirium in acute stroke. Our data can be used for audit, to plan intervention studies and inform clinical practice. The relatively high rates of delirium should be a call to action, as delirium is a serious[20] yet potentially preventable condition.[3] The frequency of delirium is similar to frequency of other stroke complications such as aspiration pneumonia and venous thromboembolism. Evidence based assessment and preventive interventions have reduced morbidity and mortality from these complications, yet at present delirium is not prioritised in stroke guidelines. Staff in the hyper-acute units should be especially vigilant as delirium seems to be most common in the first few days post ictus.

Acknowledgments: We are grateful to Doctor Mansur Kutlubaev who translated his paper.

Disclosures: None

Funding: Medical Research Scotland supported this work.Dr Quinn is supported by a joint Chief Scientist Office/Stroke Association Senior Clinical Lectureship.

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Figure Legends

Figure 1. PRISMA flow diagram

Figure 2a,b. Occurrence of delirium in acute stroke, a) forest plot b)GRADE assessment

Figure 3. Meta-regression of delirium against year of study

Table 1. Characteristics of included studies

Author and Year	Country	Sample (n)	Setting	Type of Stroke	Delirium Assessment*	Excluded stroke impairments	Excluded psychiatric syndromes
1 Alvarez-Perez 2018[40]	Portugal	1072	Stroke	All stroke	Case note review DSM	No	No
2 Caeiro 2004[23]	Portugal	218	ASU	All stroke (SAH 12.84%)	DSM	Not reported	Not reported
3 Dahl 2010[24]	Norway	178	SU	All stroke	CAM	Not reported	Not reported
4 Dostović 2008[38]	Bosnia and Herzegovia	233	SU	All stroke	DSM	Yes, aphasia	Yes, dementia
5 Fassbender 1994[25]	Germany	23	Hyperacute SU	Ischaemic stroke	DSM	No	Yes
6 Gustafson 1991[7]	Sweden	145	SU	All stroke, TIA	DSM	Yes, decreased GCS, aphasia	Not reported
7 Gustafson 1993[13]	Sweden	83	SU	Supratentorial cerebral infarction	DSM	Yes, decreased GCS	Yes
8 Henon 1999[26]	France	202	SU	All stoke	DSM	No	Yes
9 Hosoya 2018[41]	Japan	239	Stroke care centre	All stroke*	Other (ICSDC)	Not reported	Not reported
10 Infante 2017[42]	Italy	100	Tertiary stroke care centre	Acute stroke	DSM, 4AT	Yes, aphasia	Yes
11 Kara 2013[27]	Turkey	150	Neurology department	Unspecified	DSM	Yes, aphasia,	Not reported

12 Kostalova 2012[28]	Czech Republic	100	SU	All stoke	Clinical	Not reported	Yes
13 Kowalska 2018[43]	Poland	144	Neurology department	Ischaemic stroke	CAM	Yes, aphasia	Not reported
14 Kozak 2017[12]	Turkey	60	SU	All stroke	DSM, DRS	Yes, aphasia	Yes
15 Kutlubaev 2013[29]	Russia	96	SU	Unspecified	DSM	Not reported	Yes
16 Lees 2013[9]	Scotland	101	SU	All stroke	CAM	No	No
17 Lees 2017[30]	Scotland	51	SU	All stroke	CAM	No	No
18 Lim 2017[6]	Korea	576	SU	All stroke	CAM	Not reported	Not reported
19 McManus 2011[31]	England	82	SU	All stroke	CAM	Not reported	Not reported
20 Mitasova 2012[14]	Czech Republic	129	SU	All stroke	CAM	Not reported	Yes
21 Miu 2013[32]	Japan	314	SU	All stroke	CAM	Not reported	Yes
22 Mori 1987[33]	Japan	41	Neurology Service	RMCA stroke	Clinical	Yes, prior stroke, aphasia	Yes
23 Naidech 2013[10]	USA	114	SU	ICH	CAM	Not reported	Not reported

24 Nydahl 2017[39]	Germany	309	SU	All stroke	CAM	Not reported	Not reported
25 Ojagbemi 2017[34]	Nigeria	101	ASU	All stroke	CAM, DSM	Yes, aphasia	No
26 Oldenbeuving 2011[21]	Netherlands	527	SU	All stroke	CAM	Not reported	Not reported
27 Pasinska 2018[44]	Poland	750	SU	All stroke	CAM	Not reported	Not reported
28 Reding 1993[35]	USA	44	Rehabilitation unit	Unspecified	Clinical	No	No
29 Rosenthal 2018[45]	USA	150	Neuro-ICU	ICH	CAM	Not reported	Not reported
30 Sheng 2006[36]	Australia	156	SU	All stroke	Clinical	Not reported	Yes
31 Song 2018[46]†	Korea	54	SU	Unspecified	Other (DOS)	Yes, aphasia	Yes
32 Turco 2013[37]	Italy	176	Rehabilitation unit	Unspecified	CAM	No	No

* If subarachnoid haemorrhage (SAH) was included in the population, numbers are described

† two group study; the control group of normal care was used in the review

SU=stroke unit; ICH=intracerebral haemorrhage; CAM=confusion assessment method; ICSDC=Intensive care delirium screening checklist; DSM=Diagnostic and Statistics Manual; DOS=Delirium Observation Screening Scale

Table 2. Patient characteristics of included studies

Author Year	Sample Size	Mean Age	Females N (%)	Delirium cases (n)	Percentage delirium (%)
1 Alvarez-Perez 2018[40]	1072	68.0(median) range:77.0-83.0	507 (47.3%)	118	10.2
2 Caeiro 2004[23]	218	57.0±13.0	88 (40.4%)	29	13.0
3 Dahl 2010[24]	178	73.0	76 (42.7%)	18	10.0
4 Dostović 2008[38]	233	Not recorded	Not recorded	59	25.3
5 Fassbender 1994[25]	23	72.0(median) range:39.0-89.0	12 (52.2%)	9	39.0
6 Gustafson 1991[7]	145	73.0 range:40.0-101.0	55 (37.9%)	69	48.0
7 Gustafson 1993[13]	83	74.7±8.1	31 (37.3%)	35	42.0
8 Henon 1999[26]	202	75.0(median) range:45.0-101.0	105 (52.0%)	49	24.3
9 Hosoya 2018[41]	239	75.0±1.3	Not available for subgroup	80	33.5
10 Infante 2017[42]	100	79.0(Median) range:19.0-93.0	Not recorded	50	50.0
11 Kara 2013[27]	150	68.0±1.9	45 (30.0%)	42	28.0
12Kostalova 2012[28]	100	73.5±11.5	47 (47.0%)	43	43.0
13 Kowalska 2018[43]	144	69.0(median) range:63.0-79.0	61 (42.4%)	31	21.5
14 Kozak 2017[12]	60	66.2±12.5	31 (51.7%)	11	18.3
15 Kutlubaev 2013[29]	96	68.0±10.5	46 (47.9%)	22	23.0
16 Lees 2013[9]	101	74.0(median) IQR:64.0-85.0	Not available for subgroup	11	11.0
17 Lees 2017[30]	51	74.0(median) range:67.0-84.0	28 (54.9%)	8	16.0
18 Lim 2017[6]	576	65.2(median) range:23.0-93.0	208 (36.1%)	38	6.7
19 McManus 2011[31]	82	66.4±15.9	31 (37.8%)	23	28.0
20 Mitasova 2012[14]	129	71.2±11.5	57 (44.2%)	55	42.6
21 Miu 2013[32]	314	72.9±10.3	151 (48.1%)	86	27.4
22 Mori 1987[33]	41	68.2±10.9	15 (36.6%)	25	61.0
23 Naidech 2013[10]	114	63.0±13.8	52 (45.6%)	31	27.0
24 Nydahl 2017[39]	309	Not recorded	Not recorded	33	10.7
25 Ojagbemi 2017[34]	101	61.1±12.9	47 (46.5%)	33	33.3

[26] Oldenbeuving 2011[21]	527	72.0(median) range:29.0-96.0	239 (45.4%)	62	11.8
[27] Pasinska 2018[44]	750	71.8±13.1	398 (53.1%)	203	27.1
[28] Reding 1993[35]	44	66.0±13.0	25 (56.8%)	4	9.0
[29] Rosenthal 2018[45]	150	Not recorded	Not available for subgroup	53	30.0
[30] Sheng 2006[36]	156	79.2±6.7	73 (46.8%)	39	25.0
[31] Song 2018[46]	54	73.7±6.7	25 (46.3%)	13	24.0
[32] Turco 2013[37]	176	81.7±6.4	118 (67.0%)	58	33.0

Table 3. Risk of bias

	Patient Selection	Ascertainment stroke	Ascertainment delirium	Analysis
1 **Alvarez-Perez 2018**[40]				
2 **Caeiro 2004**[23]				
3 **Dahl 2010**[24]				
4 **Dostović 2008**[38]				

5 Fassbender 1994[25]				
6 Gustafson 1991[7]				
7 Gustafson 1993[13]				
8 Henon 1999[26]				
9 Hosoya 2018[41]				
10 Infante 2017[42]				
11 Kara 2013[27]				
12Kostalova 2012[28]				
13 Kowalska 2018[43]				
14 Kozak 2017[12]				
15 Kutlubaev 2013[29]				
16 Lees 2013[9]				
17 Lees 2017[30]				
18 Lim 2017[6]				
19 McManus 2011[31]				
20 Mitasova 2012[14]				
21 Miu 2013[32]				
22 Mori 1987[33]				
23 Naidech 2013[10]				
24 Nydahl 2017[39]				
25 Ojagbemi 2017[34]				
26 Oldenbeuving 2011[21]				
27 Pasinska 2018[44]				
28 Reding 1993[35]				
29 Rosenthal 2018[45]				
30 Sheng 2006[36]				
31 Song 2018[46]				
32 Turco 2013[37]				

Colour coding: green for low risk of bias, yellow for uncertain risk and red for high risk