Post-stroke Delirium: Meta-analysis of Frequency

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Abstract

Objective: To determine the frequency of post-stroke delirium by systematically reviewing original research on this topic.

Methods: MEDLINE, EMBASE, PsychINFO and the Cochrane Database of Systematic Reviews were searched for potentially relevant articles published from 1967 to March, 2014. The bibliographies of relevant articles were searched for additional references. Twelve studies met the inclusion criteria. The validity of included studies was assessed according to criteria derived from Barker et al (Barker et al, 1998). Information about diagnostic criteria for delirium,, diagnostic instruments, length and frequency of screening, population (eligible, enrolled and completed screening), age, gender, time to entering study following stroke, stroke type and location, presence of dementia and medical co morbidity, psycho-active drug use and number of patients with delirium was systematically abstracted, tabulated and synthesized according to the MOOSE guidelines for reporting of meta-analyses.

Results: There was significant heterogeneity in results of the studies of frequency of post-stroke delirium. The proportions ranged from 10% to 48%. The summary proportion was 0.24 (95% CI 0.18, 0.32). The frequency of post-stroke delirium may be related to medical co-morbidity or psycho-active drug use.

Conclusion: Post-stroke delirium may be frequent. Because of significant heterogeneity in the results of studies of frequency, the result of this review must be interpreted cautiously.

Key words: Delirium, post-stroke, incidence, prevalence, confusion

Introduction

Delirium is a neurocognitive disorder characterized by acute onset, fluctuating course and disturbances in consciousness, orientation, memory, thought, perception and behavior (DSMIV-TR). Delirium in older patients has been associated with significant increases in cognitive impairment and functional disability, length of hospital stay, institutionalization and death (Cole/93, Witlox/10).

Delirium may be frequent following stroke but reported rates vary widely. Because knowledge of the frequency of post-stroke delirium may inform decisions to develop special interventions for this disorder and because there are no systematic reviews of frequency, the objective of this study was to determine the frequency of post-stroke delirium by systematically reviewing original research on this topic. The review process, guided by the proposals of the MOOSE group for reporting of meta-analyses of observational studies, involved systematic selection of articles, abstraction of data, assessment of study validity and qualitative and quantitative synthesis of results.

Methods

Selection of articles

The selection process involved four steps. First, 4 computer databases, MEDLINE, EMBASE, PsychINFO and the Cochrane Database of Systematic Reviews were searched for potentially relevant articles published from 1967 to March 2014 using the keywords “poststroke” and “delirium” or “confusion” and “incidence” or “prevalence”. Second, relevant articles (based on independent review of the title and abstract by authors were retrieved for more detailed evaluation. Third, the bibliographies of relevant articles were searched for additional references. Finally, all relevant articles were independently screened by authors to meet the following inclusion criteria: (1) original prospective cohort study; (2) published in English; (3) used acceptable criteria for the diagnosis of delirium and (4); included information about the incidence or prevalence of post-stroke delirium. The final set of included articles was determined by consensus of authors.

Abstraction of data

Information about the study site, inclusion and exclusion criteria, diagnostic criteria for delirium,, diagnostic instruments, length and frequency of screening, population (eligible, enrolled and completed screening), age, gender, time to entering a study following stroke, stroke type and location, presence of dementia and medical comorbidity, psycho-active drug use and number of patients with delirium. Data was abstracted independently by both authors and the data included in the review was determined by consensus.

Assessment of validity

To determine validity, the methods of each study were assessed according to criteria derived from Barker et al (Barker et al, 1998): appropriate population, systemic sample, enrolment rate >75%, use of a reliable and valid diagnostic instrument (Table1). Each study was scored independently by authors with respect to meeting (+) or not meeting (-) each of the criteria. The results of the validity assessment were determined by consensus.

Data synthesis:

Qualitative: All abstracted information was tabulated. A qualitative meta-analysis was conducted by summarizing, contrasting and comparing abstracting data.

Quantitative: For each of the selected studies, the overall incidence of post-stroke delirium was verified or computed if necessary. Incidences for multiple studies were pooled in a binomial meta-analysis (5, 6). We tested study homogeneity and depending on whether homogeneity was accepted or rejected; we used the fixed or the random effect model for meta-analysis in order to calculate an overall incidence and it is 95% CI. We used the Q statistics to test between study homogeneity: homogeneity was rejected when the Q statistic p-value was less than 0.10. The meta-analysis was conducted using the R 3.1 software (7).

Results

Selection of articles:

The search strategy yielded 280 potentially relevant studies; 32 were retrieved for more detailed evaluation; 9 met the inclusion criteria (Sheng et al , 2006, Dostovic et al , 2009, McManus et al , 2009, Dahl et al , 2010, Oldenbeuving et al , 2011, Mitasova et al , 2012, Lees et al, 2013, Naidech et al , 2013, Miu et al , 2013). Twenty three studies were excluded; 6 were clinical reviews, one was a duplicate publication and sixteen did not meet one or more of the inclusion criteria. A search of the bibliographies of relevant studies yielded three additional studies that met the inclusion criteria (Gustafson et al, 1991, Gustafson et al 1993, Caeiro et al , 2004).

Assessment of validity:

All 12 studies had an appropriate population with systematic sample. In six studies, the enrolment rate was greater than 75%. Nine studies used a reliable and valid instrument to diagnose delirium

Data synthesis:

Qualitative analysis: All studies did not report on all the variables of interest (Table 3). The 12 studies were conducted in Europe (n=10), North America (n=1) or China (n=1) and, for the most part, enrolled patients admitted to university stroke units. Sample size ranged from 82 to 535 patients. Mean age ranged from 24 to 101 years. The proportion of men ranged from 46% to 63%. The length of screening ranged from 1 to 28 days and frequency of screening ranged from once during the admission to twice per day. Eight studies included patients with both intracerebral hemorrhage and cerebral infarction; two included only patients with cerebral infarction; one included only those with intracerebral hemorrhage and one study did not report the type of stroke. Eleven studies reported stroke type and location. The number of included

patients with dementia ranged from 8 to 25; two studies reported that 78 patients had cognitive decline. Nine studies reported medical co-morbidities. Four studies reported concurrent psycho-active drug use. Diagnostic instruments included the CAM (n=5), CAM –ICU (n=2), Organic Brain Syndrome Scale (n=2), Delirium Rating Scale (DRS, n=3) and DRS R-98 (n=1). Delirium was diagnosed using different versions of DSM criteria: seven studies used DSM III R; two used DSM IV; two used DSM IV R; one used both DSM IIIR and DSM IV criteria.

The frequencies of delirium varied from 10% to 48%, median 26%. Variation in reported rates could not be explained by most of the above variables. Medical comorbidity and psycho-active drug use, however, may explain some of the variation: study populations with reported high medical comorbidity and psycho-active use appeared to have higher frequencies of post-stroke delirium.

Quantitative analysis

The results of the quantitative analysis are presented in Figure 2. The Q statistic P value was <0.0001, indicating heterogeneity in reported rates of post-stroke delirium. The summary proportion with post-stroke delirium was 0.24 (95% CI 0.18, 0.32).

The frequency of post-stroke delirium may be related to medical co-morbidities and psycho-active drug use in studies that reported co-morbidities and drug use, but the timing of co-morbidity and drug use in relation to the onset of delirium is not clear.

Thus, it is unclear whether the stroke alone was the putative cause of delirium or whether delirium was due to complications of stroke (e.g. aspiration pneumonia, dehydration), other medical conditions or psycho-active drug use. Notably, there was no indication that specific diagnostic criteria, specific diagnostic instruments, greater frequency of screening or longer periods of screening identified more patients with delirium.

This review has five strengths. First, we conducted a systematic search of the literature. Second, only prospective studies were included. Third, the validity of included studies was systematically assessed. Fourth, there was a qualitative and quantitative synthesis of data and examination of study variables to try to account for variability in the study results. Finally, 3 phases of the review process (literature search, assessment of validity, data abstraction,) were conducted independently by authors who met to determine consensus.

This review has three potential limitations. First, the literature search was limited to articles published in English because we did not have the resources to translate articles written in other languages. Second, included studies did not report on all variables of interest. Third, there was significant heterogeneity in the results of the studies; it is arguable that such heterogeneity should have precluded the combining of the results of the studies.

Table 1: Estimated Incidence and weight of individual studies

				Weight of individual studies	
		proportion	95%-CI	%W(fixed)	%W(random)
1	Gustafson et al, 1991a	0.476	[0.3924; 0.5604]	10.03	8.54
2	Gustafson et al, 1991b	0.422	[0.3140; 0.5351]	5.61	8.22
3	Caeiro et al, 2004	0.133	[0.0909; 0.1854]	6.97	8.36
4	Sheng et al, 2006	0.250	[0.1842; 0.3255]	8.11	8.44
5	Dostovic et al, 2009	0.253	[0.1987; 0.3141]	12.22	8.62
6	McManus et al, 2009	0.281	[0.1868; 0.3906]	4.59	8.06
7	Dahl et al, 2010	0.101	[0.0610; 0.1551]	4.49	8.04
8	Oldenbeuving et al, 2011	0.116	[0.0900; 0.1461]	15.2	8.69
9	Mitasova et al, 2012	0.426	[0.3397; 0.5164]	8.75	8.48
10	Lees et al, 2013	0.108	[0.0571; 0.1812]	2.97	7.63
11	Naidech et al, 2013	0.316	[0.2261; 0.4180]	5.88	8.25
12	Miu et al, 2013	0.364	[0.3029; 0.4293]	15.16	8.69

Table 2: Meta Analysis summary: Incidence of Post Stroke Delirium

		Fixed effects model		Random effects model			
Effect	No. of studies	proportion	95% CI	proportion	95% CI	% of variation across studies I^2	Test of heterogeneity (Q^2) p-value
Overall effect	12	0.260	[0.2403; 0.2799]	0.249	[0.1784; 0.3366]	93.9%	< 0.0001

Figure 1: Selection of articles included in the meta-analysis

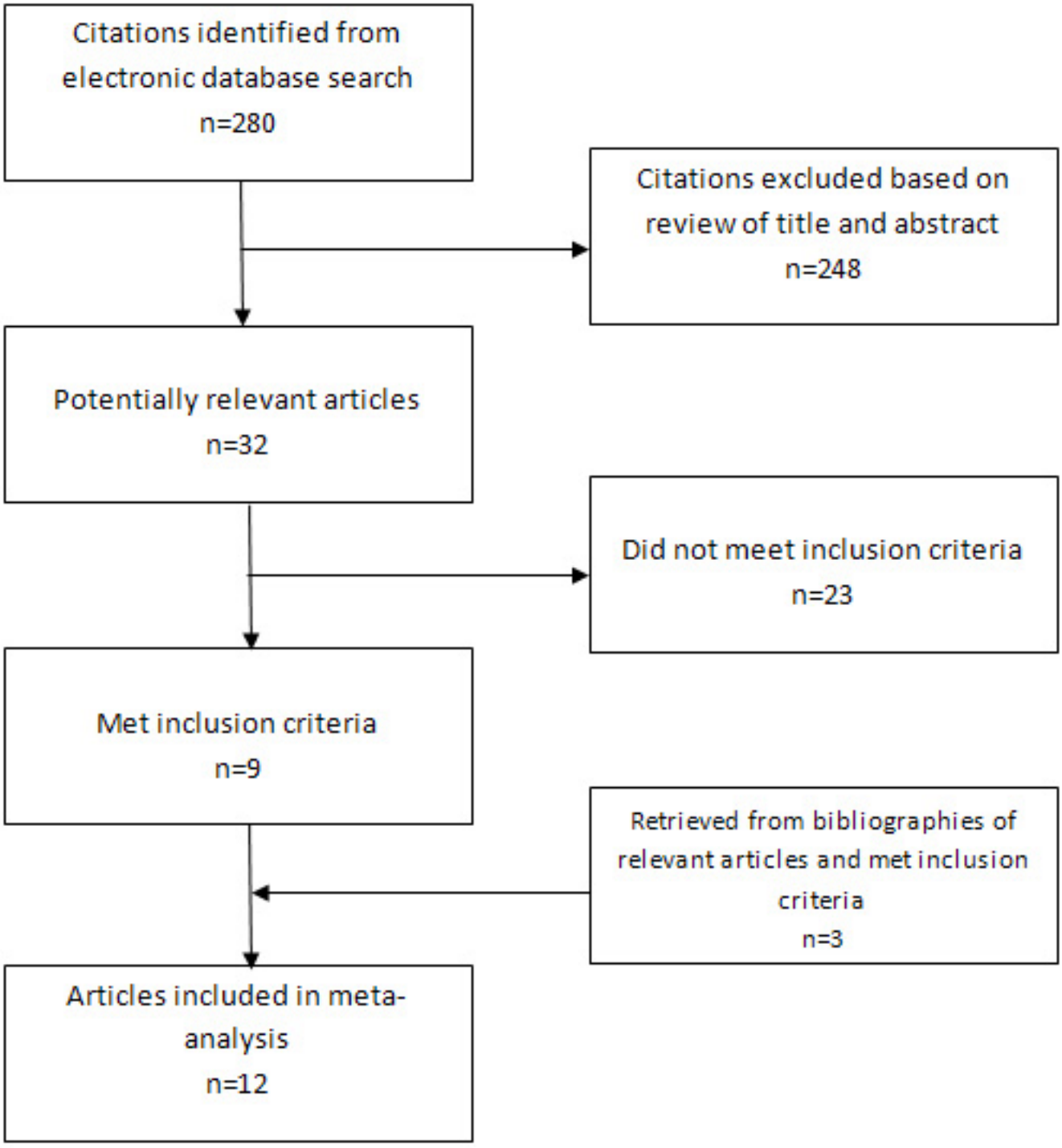

Figure 2: Forest plot of the incidence of post-stroke delirium

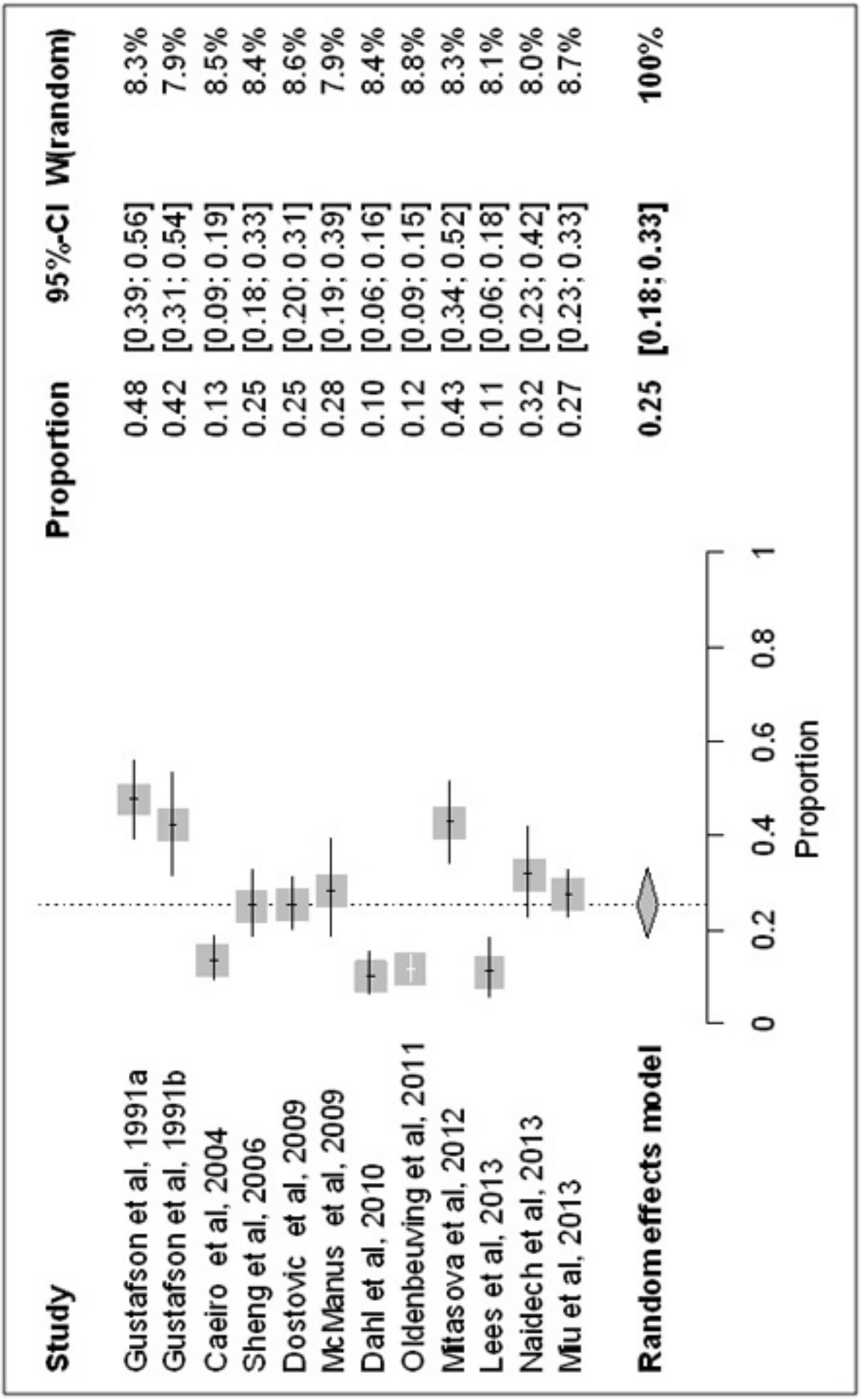

Table 3a: Studies of the Frequency of Post Stroke Delirium

Author /Year	Country	Inclusion Criteria	Exclusion Criteria	Diagnostic Criteria for delirium	Diagnostic Instruments	Frequency of screening	Length of screening (days)
Gustafson et al, 1991	Sweden	IH CI Stroke less than 1 wk prior to	SH Meningitis	DSM III R	OBSS Interview with family and staff	At least twice	7
Gustafson et al, 1991	Sweden	CI	Coma Stupor Fever Renal failure Pituitary insufficiency	DSM III R DRS>10	OBSS Interview	At least once	7
Caeiro et al, 2004	Portugal	IH CI SH	GCS <3	DSM IV TR	DRS	Once	1-4
Sheng et al, 2006	England	IH CI Aged 65+	SH TIA History of severe head injury Cerebral sinus thrombosis Neurosurgery before stroke Stroke due to tumor	DSM IV R		Once on 3rd day of admission	3
Dostovic et al, 2009	Bosnia Herzegovina	IH CI SH	GCS < 3 Recurrent stroke Epileptic seizure at onset of stroke Early stage of dementia Delirium caused by alcohol or other psychoactive substances	DSM IV DRS >16	DRS R-98	Once within 4 days	
McManus et al, 2009	England	IH CI	SH Symptoms <24 hrs GSC<8 TIA Language barrier	DSM III R	CAM DRS	Daily for 4 wks	28
Dahl et al, 2010	Norway			DSM IV DSM III R	CAM MDAS	Twice/day	
Oldenbeuving et al, 2011	Netherlands	IH CI Age 18+	SH TIA Mental Retardation Language barrier	DSM III R	CAM DRS	Between 2-4 days and 5-7 days	
Mitasova et al, 2012	Czech Republic	IH CI	SH Symptoms <24 hrs TIA History of head trauma RASS =/< 4 Tumor	DSM IV	CAM-ICU	Once/day	7
Lees et al, 2013	England	CI		DSM III R	CAM	Once	1-4
Naidech et al, 2013	USA	IH	IH due to trauma Structural lesions CI Other causes than vascular	DSM IV	CAM-ICU	Twice/day	28
Miu et al, 2013	China	IH CI SH Stroke less than 24 hrs prior to admission	Venous thrombosis TIA GSC <3 Neurosurgery Head trauma No informant	DSM III R	CAM	Once/day	1-5

Table 3b: Studies of the Frequency of Post Stroke Delirium

Author /Year	Patients Eligible	Patients Enrolled	Patients Completing Screening	Age range (mean)	M/F	Time to entering in study following a stoke (days)	Stroke Type	Stroke location
Gustafson et al, 1991	155	145		40-101 (73)	90/55	<7 (<1 in most cases)	IH 8 CI 133 TIA 21 Unknown 3	LST 65 RST 47
Gustafson et al, 1991		83		44-89 (75)	52/31	86% <2	CI 83	LH 42 RH 41
Caeiro et al, 2004	220	220	218	65-84 (57)	130/88	<1	IH 48 CI 142 SH 28	LH 71 RH 63 Brainstem-cerebellum 51
Sheng et al, 2006		186	156	65-95 (79)	83/73	3	IH 23 CI 133	CI TAC 19 PAC 45 POC 18 LI 43 Undetermined 8
Dostovic et al, 2009	561	233	233	70		<4		
McManus et al, 2009	110	82	82	24-97 (66)	51/31	<4	IH 15 CI 67	CI TAC 15 PAC 25 POC 10 LI 17
Dahl et al, 2010	200	200	178	73	102/76			
Oldenbeuving et al, 2011	535	535		29-96 (72)	288/239	<1	IH 57 CI 470	LH 272 RH 168 CI TAC 43 PAC 184 POC 87 LI 156
Mitasova et al, 2012	331	151	129	30-93 (71)	72/57	<1	IH 22 CI 107	LH 60 RH 56 IT 13 CI TAC 31 PAC 39 POC 14 LI 33
Lees et al, 2013	138		111	64-85 Median 74	55/56	1	IH 27 CI 84	CI TAC 20 PAC 29 POC 9 LI 26
Naidech et al, 2013	114	114	98	(63)	46/52		IH 114	Subcortical 59 Lober 34 IT 18 Other 3
Miu et al, 2013		314		50-94 (73)	163/151		CI 285	CI PAC 46 PAC 37 POC 14 LI 35

Table 3c: Studies of the Frequency of Post Stroke Delirium

Author /Year	Dementia (n)	Current Medical Co-morbidity	Current Psychoactive Medications Use	Number with delirium (%)
Gustafson et al, 1991	8	Cardiovascular 78 Previous delirium 14 Previous stroke 45 DM 24 Hypertension 62 Infection 12	Antipsychotic 8 Anticholinergic 16 Benzodiazepine 17 Antidepressant 8 Analgesic 21	69 (48)
Gustafson et al, 1991	2	Intercurrent infection 12 DM 12 Previous stroke 17 Previous delirium 4		35 (42)
Caeiro et al, 2004	7	DM 14 Previous stroke 40 Medical complications 47 Alcohol abuse 83		29 (13)
Sheng et al, 2006	12	Hypertension 111 A Fib 49 DM 32 Ischemic heart disease 47 Alcohol abuse 83 Left ventricular failure 13 Infection 25	Anticholinergic 5	39 (25)
Dostovic et al, 2009				59 (25)
McManus et al, 2009		Septicemia 2		23 (28)
Dahl et al, 2010	17	DM 12 Poor vision 19 Cardiac events 17 Infection 30 Urinary retention 18		18 (10)
Oldenbeuving et al, 2011	78 had cognitive decline	Infection 99 Metabolic disturbance 277 Hearing loss 31 Poor vision 21 Alcohol abuse 169		62 (12)
Mitasova et al, 2012	25		Benzodiazepine 10 Antipsychotic 40	55 (43)
Lees et al, 2013	13	Sensory impairment 16		12 (11)
Naidech et al, 2013	2	DM 22 CAD 14 A Fib 10 Hypertension 86 Pneumonia 12 Seizure 5	Benzodiazepine 56 Anticonvulsant 49	31 (32)
Miu et al, 2013	78 had pre-existing cognitive impairment	A Fib 41 Fever 107 UTI 118 Chest infection 140 Urinary retention 108		86 (27)

Legend to Table 3:

A Fib Atrial Fibrillation
BI Barthel Index
CAD Coronary Artery Disease
CAM Confusion Assessment Method
CAM-ICU Confusion Assessment Method Intensive Care Unit
CDT Clock Drawing Test
CI Cerebral Infarction
DM Diabetes Mellitus
DRS Delirium Rating Scale
DRS -R-98 Delirium Rating Scale Revised- 98
DSM Diagnostic and Statistical Manual
FIM Functional Independence Measure
GSC Glasgow Coma Scale
IQ CODE Informant Questionnaire on Cognitive Decline in the elderly
IH Intracerebral Hemorrhage
IT Infratentorial
LH Left Hemisphere
LI Lacunar infarction
LST Left-sided supratentorial
MDAS Memorial Delirium Assessment Scale
MMSE Mini–Mental State Examination
OBSS Organic Brain Syndrome Scale
PAC Partial Anterior Circulation
POC Posterior Circulation
RASS Richmond Agitation –Sedation Scale
RH Right Hemisphere
SH Subarachnoid hemorrhage

Recommendations

• The following recommendations should be considered in the design of new studies to determine the frequency of post-stroke delirium.

• The type(s) of stroke and the criteria for type should be specified as should the time to enrolment following stroke. Perhaps there should be a time limit to enrolment following stroke.

• Standardized instruments to diagnose and measure the severity of delirium would be useful.

• The frequency and length of screening for delirium should be specified.

• The number of patients, who were eligible, enrolled and completed screening should be reported.

• Stroke type and location and stroke size should be reported.

• The putative cause(s) of delirium should be assessed and reported.

• There should be measures of medical co-morbidities and psycho-active drug use that was used in the analysis of frequency of post-stroke delirium. If possible, the timing of the co-morbidity and drug use in relation to the onset of delirium should be specified.

Key points

• Post-stroke delirium appears to be frequent
• Because of significant heterogeneity in the results of studies of post-stroke delirium, the results of this review must be interpreted cautiously

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