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**REVIEW**

# Delirium post-stroke

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## Abstract

Delirium is not only one of the most common complications that older patients develop after admission to hospital but it is also one of the most serious. Although stroke is a known predisposing factor for delirium, few studies have investigated this association and results from existing studies give conflicting results with prevalence estimates ranging from 13 to 48%. The aetiology of delirium post-stroke is poorly understood. There is no consensus on the best screening tool to use to detect delirium in the post-stroke setting. Specific stroke types may be more likely to precipitate delirium than others, for example, delirium is more frequent after intracerebral haemorrhage and total anterior circulation infarction (TACI). In addition, case reports have suggested that delirium may be associated with specific lesions, for example, in the thalamus and caudate nucleus. There is a lack of intervention data in both the prevention and treatment of delirium post-stroke. However, it is known that the development of delirium post-stroke has grave prognostic implications. It is associated with longer stay in hospital, increased mortality and increased risk of institutionalisation post discharge. In this article, we review the literature to date on delirium in the acute stroke setting.

**Keywords:** *elderly, stroke, delirium, cognition*

## Introduction

Delirium is one of the most common complications that older patients develop when they are admitted to hospital, affecting up to 30% of all older medical patients [**1**]. Delirium is a severe, multi-factorial neuropsychiatric disorder with well-defined predisposing and precipitating factors. It is characterised by a disturbance of consciousness and a change in cognition that develop over a short period of time. The mental state characteristically fluctuates during the course of the day, and there is usually evidence from the history, examination or investigations that the delirium is a direct consequence of a medical condition, drug withdrawal or intoxication [**2**]. Patients who develop delirium have a high mortality, longer in-patient stay, higher complication rate, increased risk of institutionalisation and increased risk of dementia [**1, 3, 4**]. Delirium is frequently divided into (i) hyperactive, (ii) hypoactive, and (iii) mixed syndromes. Hyperactive delirium is characterised by increased motor activity with agitated behaviour. Hypoactive delirium is characterised by reduced motor behaviour and lethargy. Although hyperactive delirium has the best prognosis, hypoactive delirium is the most common form of delirium in elderly patients [**1**]. Stagno *et al.* have pointed out that the classic distinction between hyperactive and hypoactive delirium relies on motor activity, and that a more useful distinction might be between higher and lower arousal states independent of physical activity, especially after a stroke [5]. Delirium is frequently not recognised by physicians and poorly managed. Up to one-third of cases of delirium may be preventable [ **6**].

Stroke is a clinical syndrome of sudden onset of neurological impairment of presumed vascular origin. Mortality is about 15% at 1 month, 30% at 1 year and 50% at 5 years [7]. Stroke is a known risk factor for the development of delirium [**8**]. The majority of studies of delirium have reviewed mixed medical, surgical, orthopaedic or ICU patients. There have been only a small number of studies that have assessed delirium post-stroke. These studies have yielded conflicting results and have screened for delirium using different measures at different time intervals. The purpose of this article is to review the published literature on delirium in the acute stroke setting.

## Neuropathophysiology of delirium post-stroke

Although delirium has numerous potential precipitating factors (including stroke), the clinical presentation is generally similar, suggesting a common pathway in the pathogenesis of delirium. It is known that delirium is associated with generalised electroencephalogram (EEG) slowing that is consistent with widespread cortical dysfunction, which presumably accounts for the wide range of symptoms that delirious patients present with.

The pathogenesis of delirium in general remains unknown [**9**]. Various pathways have been proposed (see Table 1), these may also be important in the acute stroke setting. Several neurotransmitter systems have been implicated, in particular acetylcholine and dopamine, but also serotonin, noradrenalin and gamma amino butyric acid (GABA). Functional acetylcholine (ACh) deficiency has received most support [**10**]. ACh is involved in several functions that are affected in delirium: arousal, attention, delusions, visual hallucinations, motor activity and memory [**11**]. The evidence for ACh involvement in delirium is strong. Anticholinergic drugs can cause delirium in susceptible patients [**9, 11**]. Cholinesterase inhibition can improve anticholinergic drug–induced delirium [12]. Patients with Lewy body dementia have several features common to delirious patients: severe cognitive impairment, fluctuating symptom severity, visual hallucinations and EEG slowing [13]. Their symptoms may also respond to cholinesterase inhibitors [**14**]. An assay that measures serum anticholinergic activity (SAA) has been developed and an association has been found between SAA levels and delirium in medical in-patients [**15**]. Finally, in animal models, anticholinergic drugs cause EEG changes typical of delirium [**16**].

With respect to other neurotransmitter systems, dopamine may also be implicated [**10**]. Dopamine and ACh neurotransmitter systems interact closely and often reciprocally and an imbalance between the two could underlie delirium syndromes. There is evidence that dopamine excess can cause delirium and that dopamine antagonists, particularly neuroleptics, modify the symptoms of delirium [**16,** 17]. Glucocorticoids are also potentially implicated in delirium; and delirium has been reported in Cushing's syndrome [18].

Despite being a frequent complication of stroke, the pathophysiology of delirium in the acute stroke setting is poorly understood. There is no data on how an acute stroke affects neurotransmitter levels in the brain. Drugs with ACh activity are, however, associated with an increased risk of delirium in the acute stroke setting [**19**]. Recently, hypoperfusion in the frontal, parietal, and pontine regions have been demonstrated using single photon emission computed tomography (SPECT) scanning in patients with delirium [**20**]. It is possible that hypoperfusion, in addition to the acute brain injury, may play an important role in the onset of delirium post-stroke. In addition, one study has found an association between delirium and hypercortisolism in the acute stroke setting [**21**].

## Risk factors for the development of delirium post-stroke

Precipitating factors for delirium are numerous and generally well recognised [**1**]. However, research in this field has also focused on predisposing factors i.e. characteristics which may render a person more vulnerable to delirium in the presence of a given precipitant (Table 2). In general, the greater the load of predisposing factors for delirium, the less of an insult is needed to precipitate delirium [ **4**].

There is no predictive model presently that will identify those patients who will develop delirium post-stroke. In addition to the usual precipitating factors, the onset of delirium post-stroke is likely to be dependent on several factors unique to this clinical setting: the area of brain affected by the stroke, the extent of the stroke, the type of stroke, the extent of cerebral hypoperfusion and cerebral oedema post-stroke, in addition to the development of medical complications post-stroke e.g. aspiration. Specific stroke types may be more likely to precipitate delirium than others. Gustafson *et al.* found that a left-sided stroke is an independent risk factors for delirium development [**22**]. Caeiro *et al.* found that delirium was more

**Table 1.** Possible mechanisms in the development of delirium

| Mechanism | Example |
|---|---|
| Altered neurotransmitters | Acetylcholine |
| | Dopamine |
| | Serotonin |
| | Noradrenaline, GABA, glutamate |
| Altered hypothalamic-pituitary-adrenal axis | Hypercortisolism |
| Other mechanisms | Cytokine production, e.g. interleukin-1 |
| | Alterations to the blood–brain barrier |
| | Oxidative stress |

**Table 2.** Main predisposing factors for development of delirium

| |
|---|
| Old age |
| Male gender |
| Dementia |
| Severe illness |
| Visual impairment |
| Psychiatric illness, in particular depression |
| Alcohol excess |
| Physical frailty |
| Polypharmacy |
| Malnutrition |
| Renal impairment |
| Dehydration |

frequent with hemispherical strokes and after intracerebral haemorrhages [**23**]. Sheng *et al.* found that patients who had a cardioembolic stroke or total anterior circulation infarction (TACI) were more likely to develop delirium [**24**]. In addition, case reports have suggested that delirium may be associated with specific lesions, for example, in the thalamus and caudate nucleus [**11**]. While specific stroke types are more likely to be associated with the onset of delirium, this may be partially explained by an increased risk of medical complications, for example, infections with these stroke types, which could in turn precipitate delirium. In essence, large strokes may be more likely to cause delirium, but they also are more likely to cause medical complications, which by themselves could cause delirium. The primary precipitant for the onset of delirium may differ from case to case.

## Diagnosis of delirium post-stroke

As stroke is both a recognised predisposing and precipitating factor for delirium, all stroke patients should ideally be screened for delirium on admission and then at regular intervals. The ideal screening tool for the detection of delirium post-stroke would be quick, reliable, evidence-based, accurate, easy to use by various health professionals, applicable to all stroke patients, able to distinguish between stroke patients with delirium and stroke patients with dementia, depression or psychosis and give an estimate of delirium severity. It should also rely less on level of consciousness, verbal ability and motor disturbance, since these may be independently affected by the cerebral damage secondary to the stroke. No such tool exists. Several screening tests for delirium have been developed for use in general hospital settings. (See Appendix 1 in the supplementary data on the journal website http://www.ageing.oupjournals.org.) No instrument has been specifically designed for the acute stroke setting and there is no consensus on which of the available measures is best in the acute stroke setting.

The Mini Mental State Examination (MMSE) is a commonly used test to screen for cognitive impairment in routine clinical care [35]. However, the MMSE was not designed to distinguish between delirium and dementia, and patients who screen positive for cognitive impairment with the MMSE require further evaluation. The MMSE score is influenced by factors such as language, mood and sensory/motor function which render it unsuitable in the acute stroke setting.

The two most commonly used screening tools for delirium are the Confusion Assessment Method (CAM) [**26**] and the Delirium Rating Scale (DRS) [**25**]. The CAM was developed in 1990, to be a simple test that general health professionals could use to identify delirium rapidly and accurately. The algorithm was devised from the DSM-III-R criteria for the diagnosis of delirium. Using this algorithm, the diagnosis of delirium is based on four features: (i) acute onset and fluctuating course, and (ii) inattention with either (iii) disorganised thinking or (iv) altered level of consciousness. The CAM has high sensitivity and specificity (0.9) [**26**]. A recent study has highlighted, however, the need for appropriate training if the test is to be performed by nursing staff [36]. The CAM has potential limitations in the acute stroke setting. Feature (i) highlights the importance of acute onset of confusion with a fluctuating course. A stroke is by definition an acute vascular event, often with a change in mental state as a result of the acute brain injury. This could be mistaken for delirium. Also, there may be fluctuation in the mental status post-stroke, for example, due to the onset of cerebral oedema post-stroke which could be mistaken for delirium. Inattention (feature ii) may be difficult to ascertain in stroke patients with neglect or dysphasia. Assessing disorganised thinking after a stroke (feature iii) may be extremely difficult if dysphasia is present. Altered level of consciousness (feature iv) is common post-stroke secondary to the acute brain injury. Therefore, while the CAM is used frequently in general clinical settings, there is a need for further validation in the acute stroke setting before it can be used in that context.

The DRS is a 10-item rating scale, intended for use by medical staff with specific training [**25**]. (Please see Appendix 2 in the supplementary data on the journal website http://www.ageing.oupjournals.org.) Individual item scores are totalled to generate a 32-point scale. A cut-off of 10 is usually used to diagnose delirium. The DRS allows for estimation of delirium severity. Of the five studies to date on delirium post-stroke, two have used the DRS. One used the DRS alone [**23**], the other used the DRS in addition to clinical (DSM-IV) criteria [**37**]. The DRS and the CAM have been found to have good overall agreement in general medical in-patients [**38**] but have never been compared in the acute stroke setting.

Like the CAM, the DRS has limitations for assessing delirium post-stroke. Item 1 on the DRS (temporal onset) has the same difficulties as feature (i) of the CAM outlined above. Item 2 (perceptual disturbances), item 3 (hallucination type) and item 4 (delusions) are difficult to assess in aphasic/dysphasic patients and in patients with a reduced level of consciousness. Incorrect ascertainments may also occur with DRS item 5 (psychomotor behaviour) in patients with a reduced consciousness, similar to feature (iv) of the CAM. Regarding item 8 (sleep–wake cycle disturbance), drowsiness is common post-stroke as are stuperose/comatose periods, particularly after large cortical strokes or intracerebral hemorrhages. Finally, item 10 of the DRS (variability of symptoms) gives a score of 4 for fluctuating intensity of symptoms over a 24-h period. However, there is often fluctuation post-stroke, due to the underlying brain injury itself.

A collateral history in suspected delirious stroke patients is crucial to clarify whether dementia is also present. Pre-stroke cognitive impairment is in itself a risk factor for the development of delirium post-stroke [**20**]. Informant questionnaires such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [**39**] may be helpful adjuncts. This questionnaire applied to a close

relative has a high reliability for the presence of pre-morbid dementia between and within operators [40, 41]. The main advantage of the IQCODE in the acute stroke setting is that it requires no patient participation. A shortened version of the IQCODE with 16 questions has been shown to perform as accurately as the original longer version [42].

## Incidence of delirium post-stroke

For the purpose of this review, we used the search engine Pubmed to find all prospective studies of delirium in the acute stroke setting. The literature is limited; five studies have prospectively studied delirium post-stroke. The total number of patients evaluated in all the studies combined is 804 patients [**21–24, 37**]. In these five studies, the incidence of delirium in the acute phase of stroke varied from 13% to 48% (Table 3). Of note, the mean age in the Caeiro *et al.* study, which had the lowest incidence of delirium was 57.3 years; significantly lower than that in the other studies. Increased age is a known risk factor for delirium in all clinical settings [1]. The two studies with the highest incidence figures by Gustafson *et al.* had serial assessments. It is not surprising, in view of the fluctuating nature of delirium, that incidence rates will be higher with more frequent monitoring. By comparison, in the recent thorough review of delirium in medical in-patients, prevalence rates for delirium ranged from 10 to 31%, in studies where patients were assessed within 24 h [ **3**].

## Outcome of delirium post-stroke

Traditionally, delirium has been regarded as having a good prognosis with complete recovery if the underlying cause can be reversed [43]. In addition, delirium was felt to be a short-lived syndrome. Both these assumptions are being increasingly challenged. In studies of patients following hip replacement surgery, delirium is independently associated with poor functional outcome, death and institutionalisation [**44**, 45]. In older patients, delirium is an independent risk factor of sustained poor cognitive and functional status during the year after a medical admission [**46**]. It is also an independent marker for increased mortality at discharge and at 12 months post-discharge, for increased length of stay and institutionalisation [**3, 47**].

There are few data on the outcome of delirium post-stroke, in particular the long-term sequelae. Only one report has 12 month follow-up data [**24**]. The data that are available are summarised in Table 4 and indicate similar prognostic associations to those found in other clinical samples. Delirium post-stroke is associated with increased length of stay, increased in-patient mortality, increased risk of institutionalisation, increased need for geriatric rehabilitation, increased dependence on discharge and at 6 months, lower MMSE at 6 months and at 12 months, and higher 6 and 12 month mortality rate [**21, 24, 37**].

## Management of delirium post-stroke

To date, there have been no studies that have evaluated either the prevention or the management of delirium post-stroke. Up to one-third of delirium cases are preventable in medical wards [**6**]. Inouye *et al.* found that a multi-component intervention targeting cognitive impairment, sleep deprivation, immobility, visual and hearing impairment and dehydration reduced the incidence of delirium from 15% in the control group to 9.9% in the intervention group.

With regard to established delirium, the recent guidelines from the Royal College of Physicians give a useful overview of the important aspects of delirium management [**1**]. The most important action is the treatment of the underlying cause—this may be the stroke or it may be a complication post-stroke, for example, infection. The patient should be nursed in a good sensory environment and sedation should be used sparingly. Haloperidol is the drug of choice if sedation is needed although the evidence-base for this is weak [**1, 48**]. Prevention of complications resulting from the onset of delirium—for example, pressure sores and malnutrition—is

**Table 3.** Summary of prospective studies that have assessed delirium post-stroke

| Study | Gustafson *et al.* | Gustafson *et al.* | Henon *et al.* | Caeiro *et al.* | Sheng *et al.* |
|---|---|---|---|---|---|
| Year | 1991 | 1993 | 1999 | 2004 | 2006 |
| Country | Sweden | Sweden | France | Portugal | Australia |
| Population | Consecutive stroke patients | Consecutive ischaemic stroke patients | Consecutive stroke patients | Consecutive stroke patients | Consecutive stroke patients |
| Number of patients | 145 | 83 | 202 | 218 | 156 |
| Mean Age (range) | 73 (40–101) | 75 (44–89) | 75 (42–101) | 57.3 (24–86) | 80 (65–95) |
| Diagnostic criteria | DSM-III-R[a] | DSM-III-R | DSM-IV and DRS | DRS | DSM-IV |
| Frequency of assessments | Two assessments within first week | Before and after dexamethasone suppression test | Not specified | On admission | Within 3 days of admission |
| % Delirium | 48 | 42 | 24 | 13 | 25 |

[a] DSM-III-R refers to the revised version of the Diagnostic and Statistical Manual of Mental Disorders DSM-III criteria for the diagnosis of delirium, the precursor of DSM-IV.

Table 4. Outcome data

| Study | Year | Time period | Outcome |
|---|---|---|---|
| Gustafson *et al.* | 1991 | Up to discharge | Increased length of stay in patients with delirium (19 versus 13 days, $P<0.001$)<br>Increased institutionalisation in patients with delirium (52% of delirious patients institutionalised compared with 15% of non-delirious group)<br>Increased need for rehabilitation for delirious patients ($P<0.004$)<br>Increased mortality in patients with delirium on admission (11 of 13 deaths occurred in delirium group |
| Gustafson *et al.* | 1993 | Up to discharge | Increased mean length of stay in delirious patients (23.1 versus 15.6 days, $P<0.005$)<br>Delirious patients had higher post dexamethasone suppression test cortisol levels ($P<0.001$) |
| Henon *et al.* | 1998 | Up to discharge, in addition 6 month mortality and functional status | Delirious patients had increased length of stay ($P<0.05$), worse functional outcome at discharge ($P<0.001$) and at 6 months ($P<0.001$), lower MMSE score at 6 months ($P<0.002$) but no increase in mortality on discharge ($P = 0.828$) or at 6 months ($P = 0.38$) |
| Caeiro *et al.* | 2004 | Up to discharge | Delirious patients more likely to be dead or dependent ($P = 0.0001$) |
| Sheng *et al.* | 2006 | Up to discharge, 6 and 12 month data on mortality, MMSE, Functional Independence Measure (FIM) | Delirious patients had increased 6 month mortality ($P = 0.02$), increased 12 month mortality ($P = 0.002$) lower MMSEs at 1 month ($P<0.01$) and 12 months ($P<0.01$), lower FIMs at 1, 6 and 12 months ($P<0.01$, $P = 0.003$ and $P = 0.003$ respectively) and increased institutionalisation ($P = 0.002$) |

extremely important. It is entirely conceivable that a multi-component intervention programme that involves training of the stroke unit staff could reduce the incidence of delirium post-stroke and improve the management of established delirium.

## Conclusion

Delirium is a common complication post-stroke and is independently associated with increased mortality and morbidity. There is a need for more research to clarify the incidence, the predisposing and precipitating factors, and the prognosis in the stroke setting. It seems clear that delirium is a poor prognostic indicator post-stroke. What is less clear is whether this is because of the underlying stroke type or whether it is by itself an independent marker of poor outcome post-stoke. More research is also needed to evaluate preventative and therapeutic strategies in the stroke setting. It is unclear what the best screening tool is for delirium in the acute stroke setting or how often patients should be screened for delirium. Most screening tools for delirium require a patient to be able to speak. Perhaps a new screening tool for delirium needs to be developed for the acute stroke setting, similar to the modified CAM that has been developed and validated in the ICU setting [**49**]. All stroke units should have protocols for screening for delirium, managing patients with established delirium and for preventing delirium in at-risk patients.

## Funding

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## Conflicts of interest

None.

## Key points

- Although delirium is common post-stroke, the aetiology is unclear.
- There is no consensus on the best screening tool for delirium post-stroke.
- There is a lack of intervention data in both the treatment and prevention of delirium post-stroke.

## Supplementary data

Supplementary data for this article are available online at http://ageing.oxfordjournals.org.

## References

The long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website http://www.ageing.oupjounals.org as Appendix 3.

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