Delirium in critical care

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Delirium (side tab)

INTRODUCTION

Delirium is a common complication of critical illness. It has conventionally been regarded as an unavoidable and benign side effect of long-term sedation on an intensive care unit (ICU). However in recent years this pre-conception has been challenged by the publication of studies demonstrating poorer outcomes in ICU patients with delirium. This article will define delirium, summarise the risk factors, provide an overview of the current evidence for its detection and discuss its management.

DEFINITON AND CLASSIFICATION

The American Psychiatric Association defines delirium as 'a disturbance of consciousness, attention, cognition and perception which develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day'.[1] Delirium can be sub-classified according to aetiology using the DSM IV criteria. This is difficult to apply to the critical care population in whom a multifactorial origin is likely. A more useful clinical classification system was first described in elderly patients by Lipowski in 1983.[2] Three sub-types of delirium were described:

- **Hypoactive delirium** – Patients appear subdued, withdrawn and have a poor response to stimulus.

- **Hyperactive delirium** – Patients may display agitation or aggression and may experience delusions or hallucinations.

- **Mixed delirium** – Patients fluctuate between hypo- and hyperactive subtypes.

Ouimet et al first defined sub-syndromal delirium in a patient sub-group who displayed some features of delirium, but didn't meet the full diagnostic criteria. This introduced the concept of delirium as a spectrum of disease rather than a single entity.[3]

RISK FACTORS

Numerous risk factors have been identified for the development of delirium on the ICU.[4,-7] They are summarised in Table 1.

DIAGNOSIS

Delirium was traditionally diagnosed by a psychiatrist using DSM IV criteria. Whilst psychiatric referral can still be helpful, the development of specific delirium assessment tools, for use by the multi-disciplinary team, has greatly improved its recognition on intensive care. However delirium is probably still under-diagnosed, particularly in the hypoactive sub-type, where the more subtle features may be overlooked.

The assessment tool most commonly employed in UK clinical practice is the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).[8] Both CAM-ICU and the Intensive Care Delirium Screening Checklist (ICDSC) have been specifically validated for use on the intensive care unit.[4] Both tools are reproduced in the original version of this article (totw.anaesthesiologists.org). Both are easy and quick to perform and have good inter-observer reliability.[4] CAM-ICU, performed once every 24 hours, directly assesses the patient performing tasks to command and can be used during mechanical ventilation. ICDSC, documented every 8 hours, is more subjective as it relies on data collected during routine nursing care, without direct assessment of the patient. Patients who are experiencing isolated hallucinations may be assessed as delirium negative by CAM-ICU, but delirium positive by ICDSC.

Both CAM-ICU and ICDSC have been shown to have a high sensitivity (97%[9] and 99%[10] respectively) but CAM-ICU has a much better specificity (99%[9]) than ICDSC (64%[10]). Another study, which directly compared the performance of the two scoring systems, suggested a good level of agreement between them.[11]

INCIDENCE

For many years, the lack of a consistent definition for delirium, that could be applied to intensive care patients, hampered efforts to determine its incidence in this setting. The development of the two delirium

Summary

Delerium is a common problem in ICU patients and results in longer hospital stays, and increased morbidity and mortality. Standardised assessment tools are available and have highlighted a higher incidence than previously believed. Haloperidol is the mainstay of treatment despite lack of a firm evidence base for its use. Benzodiazepines should be avoided unless alcohol withdrawal is the cause of delirium.

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Table 1. *Risk factors for delirium on ICU.*

Medical history	Acute presentation
Age over 70	Disease severity (APACHE II score)
Hypertension	Metabolic derangement
Congestive cardiac failure	• Thyroid function
Stroke	• Glycaemic control
Epilepsy	• Hyper/hyponatraemia
Depression	• Renal function
Dementia	Thermoregulation
HIV	Sepsis
Renal impairment	Hypoxaemia
Hepatic impairment	Anxiety
Visual or hearing impairment	Uncontrolled pain

Social history	Medications
Smoker	Use of an epidural
Alcohol abuse	Opiates
Malnutrition	Benzodiazepines
	Propofol
Environmental	Anti-cholinergics
Physical restraints	
Rectal or urethral catheter	
Central venous catheter	
Sleep deprivation	

screening tools discussed has gone some way to address this issue. However, reported incidence still varies widely (16.1%-83.3%) depending on the patient demographics, illness severity and screening tool used.[9,10]

DSM IV

One study in 2001 suggested that the incidence of delirium, when assessed by two independent psycho-geriatricians using DSM-IV criteria, was as high as 81.3% in the 48 study patients.[12] During validation of the ICDSC, a psychiatrist identified delirium in 16.1% of 93 study patients using DSM IV criteria.[10]

CAM-ICU

The pilot for the CAM-ICU assessment tool found a high incidence of 83.3% in 111 study patients.[9] Subsequent studies using CAM-ICU suggest that the incidence varies between 41-74%.[6,13] This is in comparison to the data from our local mixed surgical and medical ICU in which CAM-ICU screening detected delirium in 31.7% of patients at some point in their admission.[14]

Peterson et al noted that the most common delirium subtypes were mixed (54.9%) and hypoactive (43.5%) whilst hyperactive was found to be relatively uncommon (1.6%).[15]

ICDSC

Ouimet et al[7] identified delirium in 31.8% of 764 patients in a mixed specialty intensive care unit using the ICDSC tool.

Whatever the true incidence of delirium is, it appears to be much more common than previously thought and the introduction of validated assessment tools has improved the recognition of this important condition.

PATHOPHYSIOLOGY

Currently there is no comprehensive explanation for the mechanism by which delirium occurs in the critically ill. There are however numerous hypotheses and it seems likely that its pathophysiology is multifactorial. An excellent review by Girard et al[16] covers several of the leading suggestions and these are summarised in Figure 1 (adapted from Figueroa-Ramos et al[17]):

1. Increased levels of dopamine and reduced levels of acetylcholine are thought to increase neuronal excitability and precipitate delirium. These changes may be caused by changes in the synthesis, release and inactivation of these neurotransmitters. Whether other neurotransmitters (such as GABA, endorphins, glutamate or histamine) are also involved is unknown.

2. Tryptophan is an amino acid which is actively transported across the blood brain barrier via LAT1 proteins. It is a precursor for serotonin and subsequently melatonin production. Low levels of tryptophan, and thus serotonin and melatonin, are hypothesised to cause hyperactive delirium. High levels of tryptophan, serotonin and melatonin may be responsible for hypoactive delirium.[18] It is unclear whether these effects are due to serotonin, melatonin, the neurotoxic metabolites of tryptophan or all of the above.

3. Phenylalanine is another amino acid which is actively transported across the blood brain barrier via the same transport channel as tryptophan. Consequently, high uptake of phenylalanine will compete with tryptophan and reduce levels of serotonin and melatonin. Once across the blood brain barrier, phenylalanine is converted into DOPA and subsequently dopamine, noradrenaline and adrenaline. High levels of phenylalanine have been associated with delirium,[19] but it is unclear whether this effect is due to increased levels of noradrenaline and dopamine, reduced serotonin and melatonin, or all of the above.

4. The inflammatory response to critical illness causes the release of cytokines into the circulation which results in a pro-thrombotic state. Animal studies suggest that this leads to reduced cerebral blood flow and it is possible that this could trigger delirium.

5. Engel and Romano performed EEG recordings on delirious patients in the 1940s and concluded that the slow EEG appearance they observed was characteristic of a 'derangement in the general functional metabolism of the brain'.[20] Other investigators have suggested that this might result in delirium by reducing acetylcholine levels.[21]

PREVENTION

A recent paper by Morandi et al introduces the concept of an 'ABCDE bundle' which uses an evidence-based approach in the prevention of delirium.[22] This is summarised in Figure 2.

Awake and breathing

The Awakening and Breathing Controlled Trial found that daily sedation breaks, paired with trials of spontaneous breathing, significantly improved outcome at 1 year.[23] These findings have led to the adoption of this practice in many intensive care units, although in a survey of clinical practice, the majority of practitioners admit that sedation breaks are not performed as frequently as intended.[24]

Choice of sedation

The mainstay of sedation on ICU has traditionally been propofol, benzodiazepines and opiates, all of which have been implicated in altering sleep patterns.[25] Trials involving α_2 receptor agonists (clonidine and shorter-acting dexmedetomidine) have reported a lower incidence of delirium and shorter time to extubation.[26,27] Remifentanil is a short-acting pure μ receptor agonist. Its use as a sedative agent in intensive care has been shown to reduce the time to extubation,[28] but further work is needed to assess its impact on the incidence of delirium. Interestingly, a Danish study randomised 140 mechanically ventilated patients to receive either 'no sedation' or propofol sedation with daily sedation breaks.[29] It reported shorter times to extubation and a lower
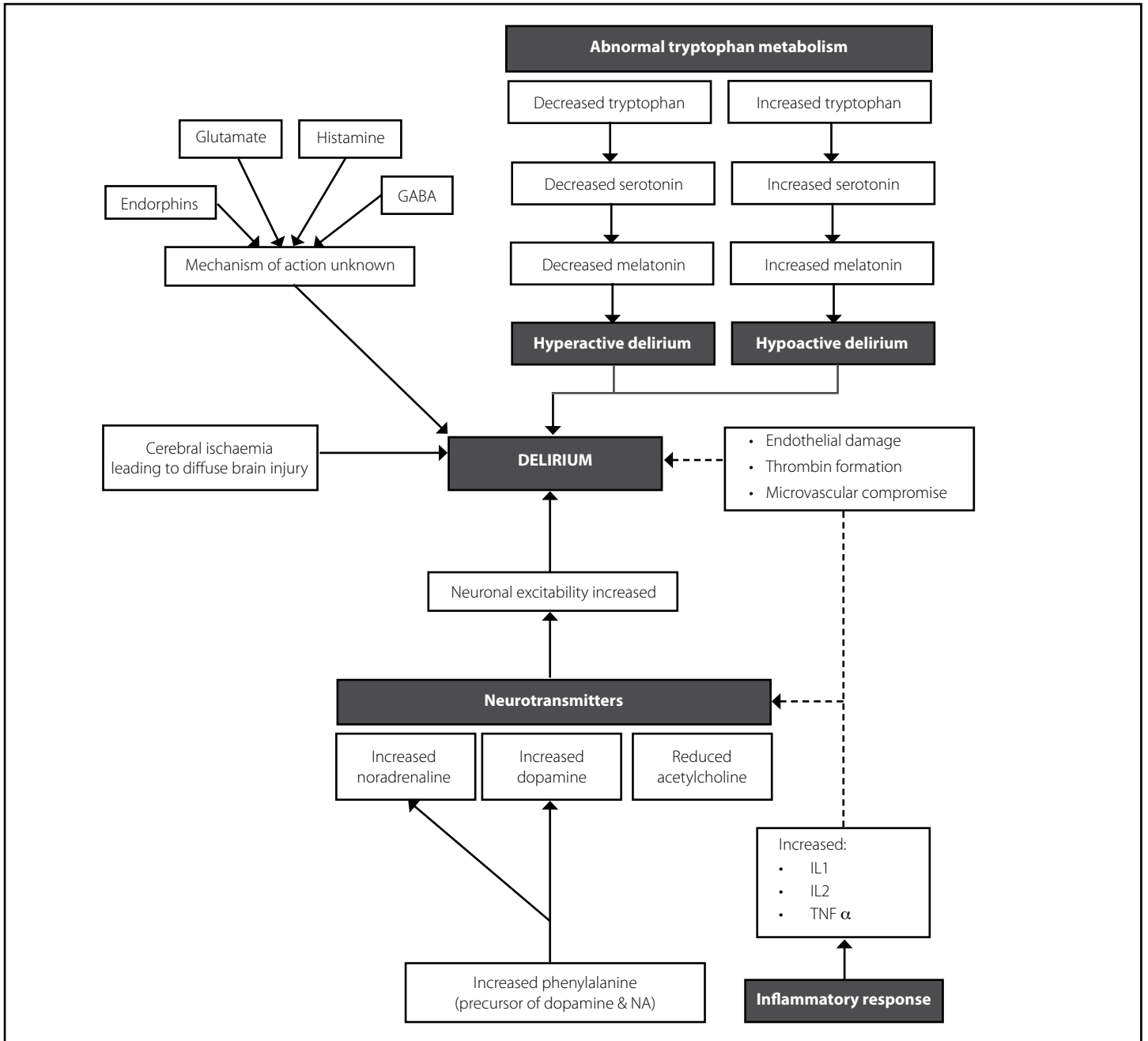

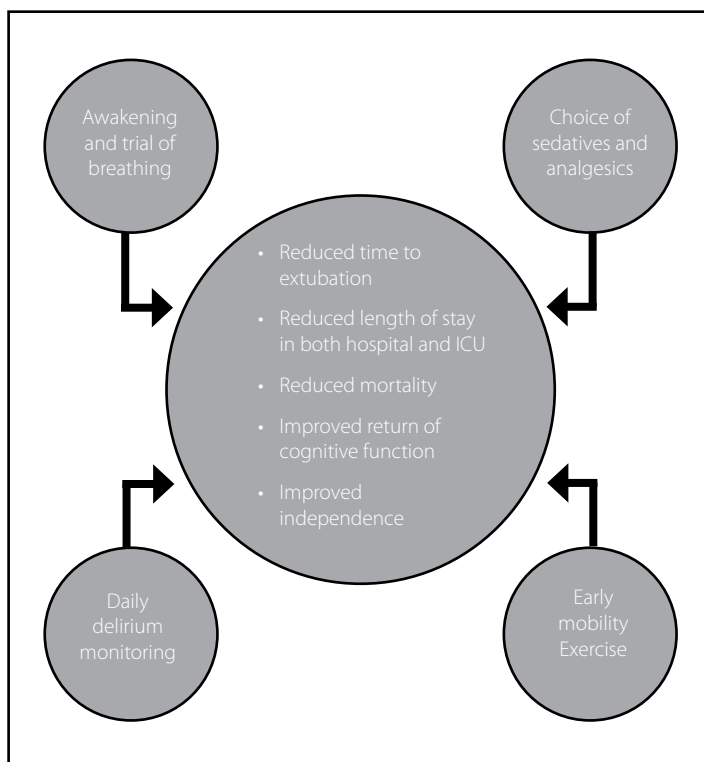**Figure 1.** *Pathophysiology of delirium[17]*

Figure 2. *ABCDE bundle[22]*

incidence of delirium, without an increase in self-extubation in the group randomised to no sedation, but it is unlikely that this practice will become widely adopted.

Daily delirium monitoring

Daily screening for delirium is important as delirium is under-diagnosed without the use of assessment tools.[30]

Early mobility and exercise

Schweickert et al demonstrated that if physical and occupational therapy was provided at the same time as a sedation break and trial of spontaneous breathing, then patients had shorter episodes of delirium and improved function at hospital discharge.[31]

Sleep

It is unclear whether sleep disruption on intensive care is a cause or a consequence of delirium. Studies have shown that the total sleep time is unaffected by sedation, but that altered REM (rapid eye movement) patterns are observed, suggesting an impact on the quality of sleep.[32] High levels of noise or ambient light, drugs, mechanical ventilation and routine patient care at inappropriate times of the day have all been associated with sleep disruption.[33]

TREATMENT: NON-PHARMACOLOGICAL

The first stage in the management of delirium is to recognise its presence by use of an appropriate assessment tool. The next stage is to review the delirium risk factors in Table 1, looking for precipitant causes that may be correctable. Some of the risk factors listed are clearly more amenable to modification than others. The more important modifiable factors are seen in Table 2.

Table 2. *Modifiable factors in delirium.*

General factors

Correct visual impairment with glasses

Correct hearing impairment with hearing aids

Medical factors

Correct metabolic derangement

Diagnose and treat sources of infection

Achieve adequate tissue oxygen delivery

Administer adequate analgesia

Remove lines and catheters promptly

Do not use physical restraints routinely but only use acutely to prevent harm

Medications

Avoid deliriogenic drugs where possible

Environmental factors

Orientate the patient regularly

Reduce noise

Reduce sleep disturbance

Mobilise where possible

TREATMENT: PHARMACOLOGICAL

There is a lack of randomised control trial evidence for pharmacological treatments for delirium on the intensive care unit. The mainstay of current therapy and that recommended by both the Intensive Care Society (UK) and the American College of Critical Care Medicine (level C recommendation) is haloperidol.[25,34] Surveys of clinical practice in the US[35] and the UK[8] revealed that the majority of clinicians use haloperidol as their first line treatment for delirium. In the UK this remains an off-licence indication for haloperidol administration.

Haloperidol

Haloperidol is a dopamine receptor (D2) antagonist and acts centrally to reduce hallucinations and delusions. It is hepatically metabolised with an elimination half-life of 10-36 hours, secondary to active metabolites. Recognised adverse effects include extra-pyramidal side effects, prolonged QT interval (which can precipitate torsades de point tachycardia) and neuroleptic malignant syndrome. The optimum dosing schedule has not yet been established by trial evidence, but a commonly used schedule is 2.5-5mg intravenously every 6 hours. Doses may need to be reduced in the elderly. It has also been used as a continuous infusion in severe cases, but this does not represent routine practice.[36]

A retrospective study of 989 mechanically ventilated patients identified a significant reduction in hospital mortality in those patients who had received haloperidol during their intensive care stay. However, the study design meant that it was not possible to identify if the indication for commencing the haloperidol was delirium.[37]

Atypical anti-psychotics

Atypical anti-psychotics (such as olanzapine, quetiapine) are also dopamine receptor (D2) antagonists, but have additional antagonistic effects on serotonin receptors (5-HT_{2A}). Enteral administration is required as there are no intravenous preparations available. They are generally metabolised in the liver and have active metabolites. Their half-lives vary according to the preparation, with quetiapine having the shortest half-life of 6 hours. The adverse effects that are most likely to be encountered include sedation and anti-cholinergic symptoms.

A randomised, but unblinded, trial of enteral olanzapine versus haloperidol in 103 patients demonstrated improvement in daily Delirium Index scores and reduced benzodiazepine administration in both trial groups, without a significant difference between them.[38]

A randomised, double blinded trial of quetiapine against placebo, with rescue haloperidol if required, found that the quetiapine group had a faster resolution of delirium.[39]

The recently published MIND study randomly assigned 101 patients to haloperidol, ziprasidone (atypical anti-psychotic) or placebo. Doses were adjusted according to the level of delirium as assessed by CAM-ICU. There was no significant difference in the number of days patients survived without delirium or coma, in any of the 3 groups in this small pilot study. A further multi-centre placebo trial is planned.[40]

Benzodiazepines

Benzodiazepines have a role in the management of delirium caused by alcohol withdrawal. However, their administration in other patient sub-groups has been identified as an independent risk factor for delirium development. Their use should therefore be avoided where possible in critically ill patients.

An adapted summary of the delirium treatment guidance produced by the UK Clinical Pharmacy Association and the Intensive Care Society is in reference 25.

PROGNOSIS

Mortality

A 6-month follow up study by Ely et al determined a statistically significantly higher 6-month mortality in ICU patients with delirium (34% v 15%, adjusted hazard ratio of 3.2).[41] Another study of 102 mechanically ventilated patients determined that ICU mortality was higher for patients with delirium compared to those without (63.6% v 32.5%, hazard ratio of 2.5).[42] Overall ICU mortality rates were lower in Ouimet et al's study of 537 patients, but it was still significantly higher in patients with delirium compared to those without (15.9% v 2.4%).[3]

Morbidity

Patients with delirium are more likely to self extubate and remove invasive medical devices.[5]

Length of stay

A study of 48 patients demonstrated that delirium significantly increased both the hospital and ICU length of stay.[12] A further study of 224 patients found that patients with delirium spent a median of 10 days longer in hospital than those without.[41] These findings are supported by Ouimet et al's study which demonstrated that even sub-syndromal delirium significantly increased length of stay.[3]

Cost

Milbrandt et al examined the cost of the hospital and ICU stays of 224 medical ICU patients in 2004.[43] They reported that patients with delirium had a significantly higher cost of care than those without and that those costs were dependent on the severity of the delirium.

Long-term cognitive impairment

A long term cohort study of 77 ICU patients determined that 79% of survivors had cognitive impairment at 3 months and 71% at 12 months.[44] A third remained severely impaired a year following ICU discharge. Delirium was identified as an independent predictor of cognitive impairment in this study. Duration of delirium also seems to be important. Patients who experienced delirium for 5 days scored almost 7 points fewer on cognitive testing, 1 year following discharge than those who experienced 1 day of delirium.

SUMMARY

Despite the surge of research activity into delirium over the past decade, the condition remains an important problem on intensive care. Standardised assessment tools validated for use in the ICU setting have been developed and have demonstrated a higher incidence of delirium than previously thought. Current treatments have a limited evidence base, particularly with respect to improving patient outcome. Whilst haloperidol currently remains the mainstay of pharmacological management, there is increasing interest in prevention of delirium by modification of its risk factors. Recent evidence suggests that delirium results in longer hospital stays, higher associated treatment costs and increased morbidity and mortality.

WEB LINKS
- www.icudelirium.org
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FURTHER READING
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