Delirium

Introduction

Delirium is the most common neurobehavioural problem encountered in general hospitals, yet is notoriously under-recognized. It is characterized by a disturbance of consciousness and change in cognition that cannot be accounted for by a prior history of dementia. This article reviews the pathophysiology, diagnosis and treatment of delirium.

Definition and epidemiology

The definition of delirium (*Table 1*) encompasses clinical features and context, and requires an underlying (proven or implied) general medical cause. This contrasts from rather non-specific terms such as 'acute confusional state', and thus is preferred.

Delirium accounts for 15–20% of all acute hospital admissions, carries significant morbidity and mortality (Trzepacz, 1996), and impairs effective communication between carers, professionals and patients. Delirium occurs at some point in 45% of cognitively impaired patients, 35% of patients following hip fracture (Bitsch et al, 2004), 60% of nursing home patients over 75 years old at any one time (Rockwood, 1993) and in 25–85% of patients with terminal cancer or acquired immunodeficiency syndrome (AIDS) within the last few weeks of life (Breitbart and Strout, 2000).

Causes of delirium

There are many precipitating factors for delirium (*Table 2*), reflecting that this is a non-specific clinical picture that can manifest in response to almost any acute or sub-acute brain insult, including metabolic and anatomical derangements.

Pathophysiology

The pathophysiology of delirium remains uncertain. No distinct anatomical site has been linked with delirium, nor any universally consistent neurochemical changes identified. It is likely that several different mechanisms operate, all leading to a secondary transient disruption of normal neuronal activity. Altered neurotransmitter concentrations have been implicated and these might contribute to a reversible dysregulation of neuronal membrane function (Brown and Boyle, 2002). Reduced cholinergic function (e.g. via anticholinergic medication (Golinger et al, 1987) or reduced production of acetylcholine with thiamine deficiency, hypoglycaemia and hypoxia) can lead to delirium (Gibson and Blass, 1976), but this is not always demonstrable.

Similarly enhanced dopaminergic transmission, e.g. in the treatment of Parkinson's disease, or through medication such as morphine, commonly causes confusion, and antidopaminergic medications, such as haloperidol, are widely used for symptomatic treatment irrespective of the cause. Serotonin (5-HT), a brainstem neurotransmitter, has raised levels in hepatic encephalopathy (Gibson and Blass, 1976), ondansetron, a 5-HT receptor blocker, has been used to reverse delirium in postcardiotomy patients (Bayindir et al, 2000). Tryptophan, a precursor to serotonin, is reduced in alcohol withdrawal, levodopa-induced delirium and postoperatively. Together with changes in melatonin, a more general 'tryptophan dysregulation' hypothesis is gaining favour (Lewis and Barnett, 2004).

GABA (γ-aminobutyric acid) has also been implicated in hepatic encephalopathy, and alcohol- and benzodiazepine-induced delirium. Flumazenil has been reported to effectively reverse symptoms in some

Table 1. *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) (DSM-1V) diagnostic criteria for delirium caused by a general medical condition

Disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention
A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia
The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day
There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition

From American Psychiatric Association (1994). The 10th revision of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) World Health Organization (1993) draws on similar criteria

Table 2. Causes of delirium

Toxic/drugs	Alcohol, anticholinergics, anticonvulsants, anti-parkinsonism drugs, illicit drugs, opiates, sedatives, steroids
Infections	Pneumonia, urinary tract sepsis, bacterial or fungal meningitis, viral encephalitis.
Metabolic	Hypoxia, hypo or hyperglycaemia, renal failure, liver failure, endocrine abnormalities (hyponatraemia, hypothyroidism, hyperthyroidism, hypo/hyperpituitarism, hyper/hypoparathyroidism, rarely porphyria and carcinoid), nutritional deficiencies (Wernicke's encephalopathy, vitamin B_{12} defiency)
Head trauma	Subdural haematoma, traumatic brain injury
Neoplastic	Primary or metastatic brain tumour, paraneoplastic disease
Vascular	Transient ischaemic attack, thromboembolic disease, myocardial infarction, congestive cardiac failure
Seizures	Ictal or post-ictal, complex partial seizures, non-convulsive status epilepticus
Autoimmune	Systemic lupus erythematosis, cerebral vasculitis

Dr Sarah Bigham *is Senior House Officer in Intensive Care, Royal Sussex County Hospital, Brighton,* **Dr Hannah R Cock** *is Honorary Consultant Neurologist, Atkinson Morley Regional Neuroscience Centre, and Senior Lecturer in Clinical Neurosciences, St Georges, University of London, London SW17 0RE*

Correspondence to: Dr HR Cock

MEDICAL EMERGENCIES

patients (Bostwick and Masterson, 1998). Raised cortisol has been linked with impaired cognition, and alterations in numerous cytokines (tumour necrosis factor, interleukin-1 and interleukin-2) have been reported, although whether these are non-specific markers of inflammation, infections and stress, or causally important is uncertain (Dunlop and Campbell, 2000).

In practice, separating out the primary causative neurochemical changes from secondary effects is rarely possible in the individual, and research in this area remains controversial (Roche, 2003).

Risk factors

The key to diagnosis is being alert to the possibility in any confused patient, and recognizing those at risk. High-risk groups are the elderly, alcohol and drug abusers, those with pre-existing brain disease, dementia, severe medical problems, visual or hearing impairment, low serum albumin, symptomatic infection, sleep deprivation, psychosocial stress, recent operations (Inouye and Charpentier, 1996), terminal cancer and AIDS.

Clinical features and diagnosis

Despite delirium having a clear definition for over 20 years (since *Diagnostic and Statistical Manual of Mental Disorders III*), hospital studies consistently show that it remains undiagnosed in 33–66% of patients (Laurila et al, 2004). This will inevitably contribute to a delay in appropriate treatments, increased health-care costs, and potentially avoidable distress for the patient, family and friends, and hospital staff. An aggressive approach to case identification reduces morbidity and mortality in a variety of settings (Bitsch et al, 2004).

The onset of delirium may be subtle or prominent depending on pre-morbid state. Three sub-groups have been described (hypoactive, hyperactive and mixed), although with the exception that alcohol and benzodiazepine withdrawal typically lead to an agitated delirium, there are no consistent correlations between underlying cause and the clinical manifestations: hypoactive, hyperactive or a mixture of the two. Hypoactive patients (24%) are characteristically lethargic, confused, hypoaroused and appear sedated. These patients are more frequently missed, possibly because they demand less attention. Hyperactive patients (30%) may display hyperarousal, hallucinations, delusions, disorientation, hyperalertness and agitation. Finally there is a mixed group, with a combination of hypoactivity and hyperactivity, which accounts for 46% (Meagher et al, 2000).

Delirium carries significant morbidity and mortality: these patients have prolonged admissions, a decline in functional ability and social independence. Other complications of delirium, e.g. pneumonia, pressure ulcers and fractures, exacerbate the condition. Hypoactive patients tend to be sicker on admission, are more likely to develop pressure ulcers and have the longest hospital stay. Hyperactivity is associated with increased falls (O'Keefe and Lavan, 1997).

Differential diagnosis

The four essential features of delirium: inattention, change in cognition, a fluctuating course and an underlying medical cause, are key to differentiating delirium from other possible conditions (e.g. dementia, psychosis or depression). Hallucinations in delirium are also common, particularly visual, in contrast to dementia (in which they are rare, with the exception of Lewy-body dementia) or psychosis (usually auditory). Dementia has a more insidious onset and patients are able to maintain their attention (assessed by counting or reciting months of the year backwards). Functional psychosis, e.g. schizophrenia, can have a variable course and in severe cases include catatonia. Memory and attention, however, tend to be intact.

The distinction between depression and delirium can sometimes be difficult, particularly in the medically unwell elderly and where the two may coexist (Farrell and Ganzini, 1995). Depression usually has an insidious onset, but can fluctuate in severity. Inattention may be prominent, and depressive pseudodementia, although uncommon, is well recognized. Any change in mood or behaviour in a medically unwell patient should prompt consideration of delirium as the cause.

Evaluation

At present, no clinical tool with sufficient sensitivity and specificity to easily diagnose delirium has been identified, and there is no substitution for careful history and examination. If the patient is unable to give a comprehensive history (as is usually the case), then a collateral history must be sought from family, care staff or the GP. This should focus on the patient's pre-morbid state, the time course of the delirium, any intercurrent illnesses or symptoms, and any recent changes in medication.

Alterations or fluctuations in consciousness are a key feature distinguishing delirium from, for example, acute psychotic illness, and as well as personal observation, can sometimes be identified by direct questioning of carers or ward staff. A mini-mental state examination (MMSE) is useful in assessing and monitoring the degree of confusion, although neither distinguish delirium from dementia, so cannot be used as a diagnostic tool. Such tests, however, have far greater inter-rater reliability than purely descriptive documentation such as 'confused', so are therefore recommended. Proforma test sheets, and more recently software for hand-held computers to facilitate the MMSE, are widely available. Inattention should be documented separately, and can be assessed by reciting numbers backwards or using a digit span test. Given the often fluctuant nature of the condition, repeated examinations at different times of day may be needed, particularly in patients with co-morbid dementia.

Basic haematology, biochemistry and urinalysis should be undertaken in all patients, and repeated if necessary, but further investigations (*Table 3*) should be guided by the clinical context. The electroencephalogram (EEG) is abnormal in 80–90% of patients with delirium, showing generalized diffused slowing but this finding will rarely alter management and is non-specific, being similar in up to 80% of patients with dementia. EEG should be confined to cases where other causes have been excluded, but is then necessary to identify non-convulsive status epilepticus.

Treatment

Identification and specific treatment of the underlying cause, where possible, is vital and will not be considered further here. Recent drug changes, infective or other metabolic causes are the most common, and often easily reversible.

Symptomatic treatment should be considered in parallel. Environmental modification to help reorientate the patient and minimize disruption to routine should be used (Inouye et al, 1999). Although this can be difficult on a busy medical ward,

Table 3. Important investigations

Blood test: full blood count, electrolytes including liver function tests and calcium, thyroid function, glucose, erythrocyte sedimentation rate, toxicology, consider vitamin B_{12} and autoimmune tests, e.g. anti-nuclear antibodies
Urinalysis
Arterial blood gas
Chest X-ray
Electrocardiogram
Computed tomography/magnetic resonance imaging of the head if focal neurology, history of trauma or no history
Lumbar puncture if the patient has an infection with no obvious source
Electoencephalogram looking for non-convulsive status epilepticus, where other causes have been excluded

this is an important factor. Calendars, clocks, maintaining normal sleep patterns, educating staff, family and friends to help orientate the patient, providing hearing aids or glasses, may all help. With agitated patients, safety (e.g. putting their mattress on the floor) also needs to be considered.

Haloperidol, a dopamine receptor blocker, is the most widely used medical treatment. Haloperidol has the advantage of having no active metabolites, rapid onset of action, multiple routes of administration and limited sedative, hypotensive and anticholinergic side-effects. Rarely, side-effects include extrapyramidal symptoms, prolonged QT interval, and abrupt withdrawal, causing rebound symptoms. Usual doses are 0.5 mg at a time, with a maximum of 10 mg within 24 hours. In the elderly, 5 mg is usually sufficient. In general, regular preventative medication, which can then be slowly withdrawn, is preferable to 'as required', as the latter may cause rebound fluctuations and increase patient distress.

Other medications to control delirium include oral atypical antipsychotics risperidone, quetiapine and olanzapine (also available intramuscularly), which have less extrapyramidal and sedative effects. Benzodiazepines are favoured in alcohol withdrawal. Lorazepam is a short-acting benzodiazepine with rapid onset, sedative effects, no active metabolites and can be given via multiple routes. With increasing doses an anxiolytic, sedative and hypnotic effect can be reached. However, benzodiazepines can sometimes exacerbate delirium, causing a 'paradoxical excitement'.

Consent

The Mental Incapacity Bill 2003 allows professionals to act in the best interests of the patient, if the patient does not have the capacity to give informed consent for treatment. To have capacity a person must be able to:

- Comprehend information relevant to the decision
- Retain this information
- Weigh the information in the balance and to arrive at choice
- Communicate the decision.

In the context of delirium, by definition the patient will be incapacitated, thus consent is rarely a problem, and so long as the best interests of the patient are clearly paramount (and not those of carers/staff) treatment and investigation can be undertaken without informed consent, although if the patient held views before becoming incapacitated then these should be respected.

Conclusions

Delirium is a well-defined common medical problem. Difficulties arise with early recognition and intervention. When diagnosed and treated appropriately, morbidity and mortality can be reduced. Future research should concentrate on reliable clinical tools for diagnosis and treatment, as well as clarifying the complicated pathophysiological processes underlying delirium. BJHM

Conflict of interest: none.

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders*. 4th edn. American Psychiatric Association , Washington DC

Bayindir O, Akpinar B, Can E et al (2000) The use of 5-HT3-receptor antagonist ondansetron for the treatment of postcardiotomy delirium. *J Cardiothorac Vasc Anaeth* **14:** 288–92

Bitsch M, Foss NB, Kristensen BB et al (2004) Pathogenesis of and management strategies for postoperative delirium after hip fracture. *Acta Orthop Scand* **75**(4): 375–7

Bostwick JM, Masterson BJ (1998) Psychopharmacological treatment of delirium to restore mental capacity. *Psychosomatics* **39:** 112–17

Breitbart W, Strout D (2000) Delirium in the terminally ill. *Clin Geriatr Med* **16:** 357–72

Brown T, Boyle M (2002) ABC of psychological medicine: Delirium. *BMJ* **325:** 644–7

Dunlop RJ, Campbell CW (2000) Cytokines and advanced cancer. *J Pain Symptom Manage* **20:** 214–32

Farrell KR, Ganzini L (1995) Misdiagnosing delirium as depression in medically ill elderly patients. *Arch Int Med* **155:** 2459–64

Gibson GE, Blass J (1976) Impaired synthesis of acetylcholine in brain accompanying mild hypoxia and hypoglycaemia. *J Neurochem* **27:** 37–42

Golinger R, Peet T, Tune L (1987) Associated elevated plasma anticholinergic activity with delirium in surgical patients. *Am J Psychiatry* **144:** 1218–20

Inouye SK, Charpentier PA (1996) Precipitating factors for delirium in hospitalised elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* **275***:* 852–7

Inouye SK, Bogardus ST, Charpentier PA et al (1999) A multicomponent intervention to prevent delirium in hospitalised older patients. *N Engl J Med* **340:** 669–76

Laurila JV, Pitkala KH, Strandberg TE et al (2004) Detection and documentation of dementia and delirium in acute geriatric wards. *Gen Hosp Psychiatry* **26**(1): 31–5

Lewis MC, Barnett SR (2004) Postoperative delirium: the tryptophan dysregulation model. *Med Hypothesis* **63**(3): 402–6

Meagher DJ, O'Hanlon D, O'Mahony E et al (2000) Relationship between symptoms and motoric subtype of delirium. *J Neuropsychiatry Clin Neuroscience* **12:** 51–6

O'Keefe ST, Lavan JN (1997) The prognostic significance of delirium in older hospital patients. *J Am Geriatric Soc* **45:** 174–8

Roche V (2003) Southern Western Internal Medicine Conference. Etiology and management of Delirium. *Am J Med Sci* **325**(1): 20–30

Rockwood K (1993) The occurrence and duration of symptoms in elderly patients with delirium. *J Gerontology* **48** (4): M162–6

Trzepacz PT (1996) Delerium: advances in diagnosis, pathophysiology, and treatment. *Psychiatr Clin North Am* **19:** 429–48

World Health Organisation (1993) *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research.* World Health Organisation, Geneva

KEY POINTS

- Delirium is a very common condition in hospitalized patients, and often under-diagnosed.
- Delirium is associated with poor outcome, and prompt recognition, investigation and treatment are key.
- Differentiation from other conditions such as dementia, depression or psychosis can sometimes be difficult, and may required repeated examinations and assessments.
- The four essential features of delirium are inattention, change in cognition, an acute and fluctuating course, and an underlying medical cause.
- The pathophysiology is not well understood, and probably multifactorial.
- High-risk groups are the elderly, severely ill patients and alcohol and drug abusers.
- Treatment requires a combination of treating the underlying cause, environmental measures and antipsychotic drugs.