CHAPTER 21.

DELIRIUM

Introduction

Delirium is from Latin and literally means the individual is not at the top of his/her form and travelling at a lower level than normal [de – (off, away from) + lira (a ridge between ploughed furrows)].

"Delirium is a common clinical syndrome characterized by inattention and acute cognitive dysfunction" (Fong et al, 2009a). Inattention means poor ability to concentrate.

Delirium can be an outcome of a general medical conditions, head injury and drug intoxication or withdrawal. It may be the result of the dysfunction of various bodily organs such as kidneys and liver, but it may also be the result of primary pathological processes in the brain.

Delirium is not fully understood. There are problems with terminology; delirium synonyms have included 'acute confusional state', 'organic brain syndrome', and even, 'reversible dementia'.

Delirium is associated with death (Inouye, 2006). Hospitalized patients $\geq$ 65 years who experience delirium (compared to those who do not) are at greater risk of mortality ($p<.0001$) over the subsequent 5 years.

It is a distressing (to patients, family and staff) and financially costly.

Delirium is seen more commonly on medical and surgical wards than psychiatric wards. It complicates the hospital stays of 20% of the people over the age of 65 years, and is found in up to 87% of older patients in intensive care wards (Pisani et al, 2003).

DSM-5 criteria Delirium

A. Disturbance of attention (reduced ability to focus, sustain, or shift attention).
B. Develops over a short time (hours or a few days) – a change from baseline attention and awareness, fluctuates in severity in the course of a day.
C. An additional disturbance in cognition (such as memory deficit, disorientation, language disturbance).

Sub-types of delirium

Three clinical subtypes of delirium, based on arousal and psychomotor behaviour are described (Trezepacz et al, 1999)

1. Hyperactive (hyperaroused, hyperalert, or agitated)
2. Hypoactive (hypoaroused, hypoalert, or lethargic)
3. Mixed (alternating features of hyperactive and hypoactive types)

Hyperactive symptoms	Hypoactive symptoms
Hypervigilance	Unawareness
Restlessness	Decreased alertness
Fast or loud speech	Lethargy
Irritability	Slowed movements
Combativeness	Staring
Impatience	Apathy
Swearing	
Singing	
Laughing	
Uncooperativeness	
Euphoria	
Anger	
Wandering	
Easy startling	
Fast motor responses	
Distractibility	
Tangentiality	
Nightmares	
Persistent thoughts	

While the "classic" presentation of delirium is considered to be the wildly agitated patient, the hyperactive type represents only about 25% of cases. Over half all delirious patients have the hypoactive "quite" type. These people attract less attention and may pass undiagnosed - this (hypoactive) type has the poorer prognosis.

Another "classic" feature is widely believed to be "sundowning", by which is meant, the mental status deteriorates in the evening. Recent work, however, demonstrated that more symptoms were demonstrated in the morning (47%) than in the afternoon, evening and night (37%).

Confusion Assessment Method (CAM)

CAM (Inouye et al, 1990) is a remarkable instrument – it is a brief structured assessment - with a sensitivity of 94%, a specificity of 89%, and moderate-to-high inter-rater reliability. It is simple and widely used by nursing staff.

Four questions to be answered with: Yes/No?
The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

1. ***The history of acute onset and fluctuating course***
   Obtained from family member or nurse as is shown by positive response to the questions:
   Is there evidence of acute change in mental status from the patient's baseline?
   Does the (abnormal) behaviour fluctuate during the day, that is, does it tend to come and go or increase or decrease in severity?

2. ***Inattention***
   This feature is shown by a positive response to the following question:
   Does the patient have difficulty focusing attention such as are they easily distracted or do they have difficulty keeping track of what is being said?

3. ***Disorganised thinking***
   This feature is shown by a positive response to the following questions:
   In the patient's thinking disorganised or incoherent?
   I the conversation rambling or incoherent, unclear with an illogical flow of ideas or unpredictable switching from one subject to another?

4. ***Altered level of consciousness***
   This feature is shown by any answer other than 'alert' to the following question:
   Overall, how would you rate the patient's level of consciousness? (alert [normal], vigilant [hyper alert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unrousable])

Testing attention

A commonly used method of testing attention is to ask the patient to perform the serial 7's test. Rudolph & Marcantonio (2003) make the point that this test requires more calculation skill than attention. Accordingly, they recommend the following:

- Days of the week backwards
- Months of the year backwards
- Digit span (forwards and backwards)
- Spell "world" backwards
- Trailmaking test A

Predisposing and precipitating factors

Delirium is a difficult topic, both theoretically and clinically. A list of predisposing and precipitating factors is valuable.

Placement under these headings is somewhat arbitrary, and there is overlap. The large number of factors sets the scene for the next section which points out that multiple factors are involved in most cases.

In the predisposing factors listed below, we learn that age is a risk factor – in ICU patients, the probability of developing delirium increases by 2% per year after the age of 65 years. We also not that any cognitive loss or dementia are potent risk factors. Any reduction of fitness makes the organism vulnerable.

Predisposing factors

- Advanced age
- Dementia
- Functional impairment in activities of daily living
- Medical comorbidity
- History of alcohol abuse
- Male gender
- Sensory impairment (blindness, deafness)

Precipitating factors

- Acute myocardial events
- Acute pulmonary events
- Bed rest
- Fluid and electrolyte disturbance (including dehydration)
- Drug withdrawal (sedatives, alcohol)
- Infection (especially respiratory, urinary)
- Medications (wide range, esp. psychoactive, anticholinergic and opioids)
- Uncontrolled pain
- Urinary retention, faecal impaction
- Indwelling devices (urinary catheters)
- Severe anaemia
- Use of restraints
- Intracranial events (stroke, bleeding, infection)

Pathophysiology

A range of different pathological circumstances give rise to delirium. The systems of the body interact – a difficulty in one system soon embarrasses another, which then contributes to the dysfunction and clinical picture. A single, universal pathophysiology does not exist.

One study found 16% of a sample had a single etiologic factor, 27% had two, and 90% had up to four etiologic factors (Camus et al, 2000). Where multiple factors are identified, they may have arisen independently or as consequence.

Nevertheless, in more than half the cases, the aetiology remains unknown (Stiefel et al, 1992).

Maldonado (2017) describes a System Integration Failure Hypothesis of delirium. This is an amazingly complex account of how the various human physiological systems interact – illustrating the mechanisms by which delirium may be provoked delirium, and each other.

He thereby unites 1) Neuroinflammatory hypothesis, 2) Oxidative stress hypothesis, 3) Neuroendocrine hypothesis, 4) Melatonin dysregulation hypothesis, 5) Neurotransmission hypothesis, and 6) Network disconnectivity hypothesis.

Under-pinning findings include (Maldonado, 2013):

1. Leaky blood-brain barrier. Recent evidence suggests the blood-brain barrier becomes leaky or disrupted as the brain ages, allowing exposure to drugs and toxins. Also as a result of distal imflammation.

2. Cholinergic deficiency. This is one of the best documented mechanisms. It is seen in overdose of anticholinergic drugs, such as atropine. It may also be seen with the use of drugs not primarily classified as anticholinergics, but with clear cholinergic action: antihistamines, some opioids and antidepressants. However, significant anticholinergic activity has been found in the serum of patients who are not taking drugs with anticholinergic properties - this suggests an endogenous anticholinergic activity may predispose certain patients to delirium.

3. Imbalance of neurotransmitter production. Serotonin is a major CNS neurotransmitter. Production depends on transport of tryptophan across the blood-brain barrier. Tryptophan competes with the amino acid phenylalanine for transport across the blood-brain barrier. Disturbance of the tryptophan: phenalanine ratio may increase or decrease the level of serotonin resulting in delirium. Disturbance of the tryptophan: phenalanine ratio has been observed in post traumatic states and other medical and surgical conditions.

4. Inflammation. Trauma and infection leads to increased production of proinflammatory cytokines, which may produce delirium. Peripherally secreted cytokines can cause responses from microglia, causing inflammation of the brain. Cytokines affect the synthesis and release of a wide range of neurotransmitters and also have neurotoxic (Cavallazzi et al, 2013).

5. Elevated cortisol. Acute stress has been hypothesized as a cause of delirium. This is consistent with the notion that elevated cortisol seen in PTSD results in hippocampal shrinkage. The role of cortisol in delirium is under investigation (Maclullich et al, 2008).

6. Neuronal injury caused by a variety of metabolic or ischaemic insults.

7. Other neurotransmitter abnormalities associated with delirium include elevated dopamine function (haloperidol is effective in controlling symptoms). Possibly, also NA and GABA.

Differential diagnosis

The main disorders to consider include dementia (Chapter 20), depression, anxiety and other psychotic disorders (including 'Delirious mania, see below).

Hypoactive delirium may look like severe depression, with lack of movement and interest in the surroundings. (This carries the risk of adding an antidepressant medication which may compound the problem (Rathier & Baker, 2011)). Depression is usually preceded by a history of mood disorder, and the thought content may be helpful. Hyperactive delirium is rarely taken to be agitated depression, however, it may be difficult to exclude a severe anxiety disorder. Hallucinations and delusions associated with delirium may suggest a "functional" psychosis, but the picture is clarified by looking for clouding of consciousness (concentration), cognitive difficulties (memory and orientation difficulties) and a fluctuating course.

Delirium and dementia

Where delirium is termed acute brain failure/disorder, dementia is termed chronic brain failure/disorder.

These conditions are interrelated. Dementia is a risk factor for delirium; over half the patients who develop delirium have an underlying dementia. And, acute delirium may leave dementia in its wake. Recent studies indicate that delirium, once considered a brief disorder, may persist for months or even years (McCusker et al, 2003). The line between persistent delirium and dementia is blurred.

Both conditions are associated with decreased cerebral metabolism, cholinergic deficiency and inflammation (Eikelenboom & Hoogendijk, 1999). Imaging studies demonstrate both conditions feature regions of hypoperfusion (Yokota et al, 2003). It is remembered from Chapter 20 that in dementia with Lewy bodies, fluctuating cognition and hallucinations are core features. Thus, similar mechanisms may be involved.

An episode of delirium can dramatically worsen the trajectory of an underlying dementia (Inouye, 2006; Fong et al, 2009b).

Prevention

'Multifactorial interventions' refers to efforts to prevent and treat delirium by multidisciplinary staff, who address the risk factors of delirium as soon as the elderly patient presents to the acute care environment – the activities provided include constant patient orientation, addressing visual and hearing needs, addressing bladder and bowel function, pain management, etc. Oberai et al (2018) reviewed studies of multicomponent intervention and found a reduction in reducing incidence.

In efforts to prevent delirium, the following points are recommended:

- Routine cognitive testing on admission and during hospitalization
- Ensure the continued use of glasses and hearing aids as appropriate

- Ensure adequate intake of fluids and nutrition by providing assistance as necessary
- Early identification and treatment of dehydration
- Early mobilization
- Avoid physical restraints (Fick, 2011).
- Involving family members or one-to-one nursing to calm and reorientate. (Freter & Rockwood, 2004)
- Cease or minimize use of potentially problematic medications -
    - Minimize benzodiazepine use; dexmedetomidine, an alpha-adrenergic receptor agonist, appears to be a suitable sedative alternative (Riker & Fraser, 2011).
    - Adequate pain relief - inadequately treated pain increases the likelihood of delirium. With respect to older person post hip surgery management, opioid use is not associated with delirium in patients with or without dementia (Sieber et al, 2011).
- Prophylactic perioperatively antipsychotics (haloperidol, risperidone, olanzapine) use has been successful, but is not yet routinely recommended (Cerejeira &Mukaetova-Ladinska, 2011; van den Boogaard, et al, 2013).

Management

'Multifactorial interventions' has some ability to prevent delirium, but once established, this approach does not significantly reduce the severity or duration (Cerveira et al 2017; Oberai et al 2018)

Investigations are guided by a comprehensive assessment of the patient, advice on baseline functioning from people who know the patient, and a careful review of prescribed medications (with particular attention to recent additions and changes).

Basic laboratory testing includes complete blood count, electrolytes and renal function tests, oxygen saturation, ECG, urinalysis and chest X-ray. Somewhat unexpectedly, intracranial factors are rare and should be considered only when all other factors have been excluded, or if there are focal neurological signs.

Curative pharmacological agents such as antibiotics should be applied as indicated.

The presence of family members at the bed-side is reassuring. One-to-one nursing is recommended if possible.

Anxiolytic medication (particularly benzodiazepine) is best avoided, because of the real risk of worsening matters.

Symptom controlling pharmacological agents may be necessary with combative and disturbed behaviour.

Quetiapine, however, has recently been described as being effective and safe for the treatment of delirium in both general medicine and intensive care units (Hawkins et al, 2013). Olanzapine and haloperidol decrease the severity, and Rivastigmine (an anticholinesterase inhibitor) reduces the duration of delirium (Cerveira et al, 2017)

[Delirious mania
Delirious mania is a unique condition is so far as the only insult to the brain is a psychiatric disorder. The condition may be overlooked because it is difficult to communicate with highly disturbed manic people. However, up to 15% of people with mania may be delirious. ECT may be indicated. Benzodiazepines are generally considered contra-indicated in delirium, however, in delirious mania, intravenous lorazepam can have dramatic, beneficial effects (Jacobowski et al, 2013).]

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