Delirium: a synthesis of current knowledge

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Introduction

Worldwide, it is estimated that the prevalence of delirium is 0.4\% in the general population, increasing to 1\% in the population above 55 years of age.\textsuperscript{1} In hospital, delirium is more common, occurring in up to 22\% of patients attending medical departments, 11–35\% in surgical departments and up to 80\% of patients in intensive care units.\textsuperscript{2,3} Therefore, delirium in older patients is a frequent complication in patients in hospital and is associated with negative outcomes, including a longer hospital stay, increased risk of complications and higher mortality, both during hospitalisation and afterwards, loss of independence and increased risk of cognitive decline.\textsuperscript{4–6} Given that it has been demonstrated that delirium can be prevented to a significant extent by a focused approach, delirium can no longer be seen as an inevitable complication of illness and its incidence gives a helpful marker of quality of care.\textsuperscript{7}

Diagnosis

Delirium became a more clearly defined entity following its inclusion in the third edition of the Diagnostic and Statistical Manual (DSM-III) of the American Psychiatric Association in 1980. Since then, subtle changes have been made in the definition of the syndrome. In 2013, the criteria for delirium in DSM-V underwent a substantial change by narrowing the spectrum of arousal states in which delirium can be identified (Table 1). Many professional bodies, including the European Delirium Association, are concerned that patients who are not comatose, but who are too drowsy to demonstrate inattention by interview, might be inaccurately classified as not having delirium and therefore might miss out on appropriate diagnostic work up and treatment. Apart from this consideration, although the DSM-V definition is useful, it can still be difficult to make a clear-cut diagnosis and differences remain among research groups as to the operationalisation of the DSM criteria. Additionally, different subtypes exist without an uniform diagnosis.\textsuperscript{8} Also, the terms ‘subsyndromal delirium’ and ‘persistent delirium’ are not yet a part of agreed criteria, but are frequently used descriptors for certain manifestations of delirium.\textsuperscript{9,10} In summary, delirium should always be considered in any patient where changes in cognition develop over a matter of days with impairment in attention: if in doubt, there should be a low threshold for seeking a specialist opinion (eg from a geriatrician, old-age psychiatrist or neurologist) to verify the diagnosis and to assist in the detection of underlying somatic factors.

Risk factors

Previously, risk factors were divided into predisposing and precipitating factors by Inouye.\textsuperscript{11} Risk factors were mainly identified in cross-sectional research, which limits the possibility to link the time course of factors in the aetiology of delirium. Knowledge of the predisposing and precipitating factors is relevant for clinical practice. Fig 1 shows the relationship between predisposing and precipitating factors in the risk for delirium as proposed by Inouye.\textsuperscript{6,12} Whereas a person with many predisposing factors will only need a minor trigger to develop delirium (eg an older patient with dementia experiencing a mild urinary tract infection), a person without predisposing factors requires a more severe trigger (eg a young patient with severe sepsis in the intensive care unit). This interaction can help in the search for precipitating factors for individual patients. When a relatively healthy person develops delirium, one should keep on searching until a serious underlying problem is identified. The exact cause often remains uncertain and is multifactorial in 50\% of cases.\textsuperscript{13} The precipitating factor(s) can include any illness, medication effect or surgical procedure, but in older and more frail populations, the most common cause(s) are infections, metabolic abnormalities, adverse drug effects and cardiovascular events.\textsuperscript{14} Recent literature splits risk factors into modifiable and non-modifiable, an approach that makes sense from the perspective

Fig 1. Relationship between predisposing and precipitating factors. Increasing darkness implicates a higher risk of delirium. Reproduced with permission from van Munster et al (2009).\textsuperscript{12}
of prevention. Risk factors identified consistently across several studies include cognitive impairment and/or dementia, higher age, severity of disease, infection, fracture at admission, vision impairment and physical restraints. In specific patient populations, further disease-specific risk factors can be identified: in stroke, for example, aphasia, neglect or dysphagia are risk factors for delirium. With increasing age, the duration of delirium is generally longer and the symptoms more severe. Other factors associated with a more serious course are admission to an expensive medical unit and a higher number of concurrent medical illnesses.20

Pathophysiological mechanisms

Given the broad range, and often combinations, of multiple precipitating and predisposing factors that lead to the same syndrome, involvement of various interacting systems in the brain with a final common pathway seems to be the most plausible rationale for the syndrome of delirium. The current leading candidate for the final pathway is the neurotransmitter system of relative acetylcholine deficiency and dopamine excess. Cholinergic depletion has been shown to predispose to the development of acute cognitive deficits following systemic inflammatory insult. Peripheral inflammation can activate the central nervous system (CNS) by several routes, including the circumventricular organs, vagal afferents and the brain endothelium. These peripheral inflammatory signals also have severe deleterious effects on brain function when occurring in old age or in the presence of neurodegenerative disease. In these circumstances, the cholinergic inhibition of primed microglia is reduced, leading to an exaggerated inflammatory cascade that could also account for the development of long-term cognitive impairment.

Treatment

The treatment of delirium is generally divided into three steps. The first and most important step is to treat the underlying disease or diseases that precipitate the delirium. In addition, there is an increasing evidence base for the utility of non-pharmacological measures for the prevention and treatment of delirium. Structured multidisciplinary interventions reduce the incidence and duration of delirium in hospital and lessen functional decline in older patients. The intervention should be focussed on multiple domains (ie orientation, sensory deprivation, sleep and/or circadian rhythm, arousal, mobilisation, hydration, nutrition and medication use). Participation of a family member in the care for patients with delirium (or at high risk of developing delirium), including making it possible for them to stay overnight with the patient, is an easy intervention with a large impact. The multicomponent intervention should be implemented throughout the hospital on a 24 hour per day, 7 day per week basis and actively promoted with patients at risk for delirium. Finally, for patients who are in psychic distress or are too restless to be treated adequately, despite applying the interventions outlined above, antipsychotics should be started at the lowest possible dose and for the shortest possible time period. Evidence for the efficacy of antipsychotic treatment is limited in delirium.24 Moreover, antipsychotics have significant adverse effects, even when prescribed for short periods, including parkinsonism and an increased risk of stroke. There is no evidence to support the use of benzodiazepines among patients in hospital for the treatment of delirium that is not related to alcohol withdrawal.

Prevention

Prevention of delirium can be either primary or secondary. Limited evidence is available for the pharmaceutical prevention of delirium and reduction of severity with antipsychotics, and they are not currently recommended for any patient with, or at risk of, delirium. Recent studies showed promising effects of melatonin for delirium. There is not enough evidence for single-component interventions, such as hydration, although music therapy seems to show promise in the reduction of the incidence of delirium. The multiple modifiable risk factors for delirium suggest that multifactorial interventions designed to reduce the impact of selected risk factors are associated with a reduction in delirium incidence and in its duration. These interventions seem to be cost effective for older patients at intermediate or high risk of delirium who are admitted to general medicine services, or in older patients admitted with hip fracture. Ideally, all patients in hospital should be screened for risk of developing delirium. However, the introduction of delirium prevention protocols into routine care has been slow.

### Table 1. Summarised criteria for delirium from recent versions of the *Diagnostic and Statistical Manual of Mental Disorders*.

<table>
<thead>
<tr>
<th>DSM IV-R criteria</th>
<th>DSM 5 criteria</th>
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<tbody>
<tr>
<td>A Disturbance of consciousness with reduced attention</td>
<td>A Disturbance in attention</td>
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<tr>
<td>B Change in cognition or a new perceptual disturbance</td>
<td>C Change in an additional cognitive domain, not accounted for by another neurocognitive disorder</td>
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<tr>
<td>C Acute development and fluctuation over 1 day</td>
<td>B Acute development and fluctuation over a day and not solely the result of another neurocognitive disorder</td>
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<tr>
<td>D Caused by a somatic factor, medication intoxication or withdrawal</td>
<td>D Disturbances in A and C must not be occurring in the context of a severely reduced level of arousal, such as coma</td>
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**Note:** DSM = Diagnostic and Statistical Manual of Mental Disorders. Changes in DSM 5 from DSM IV shown in italics.
worldwide and might require incentivisation by governments or insurance companies to be more widely implemented.

After recovery from delirium, patients should be followed up by a geriatrician or general practitioner for several reasons. In the first instance, they might require counselling about the episode, given that the subjective experience of delirium can be traumatic. In addition, they should be reassessed for possible cognitive impairment because their delirium might have occurred against a background of previously undiagnosed baseline mild cognitive impairment or dementia. Equally, there is a role for secondary prevention by ameliorating risk factors for a further episode (i.e., through stopping or reducing anticholinergic medications and optimising vision and hearing). A systematic intervention in older patients after a delirious state found that institutionalisation could be delayed by the implementation of periods of rehabilitation and case management.

**Implementation**

The experience of patients with delirium has gained more prominence in the biomedical literature and the public domain worldwide. Our group has produced a DVD with subtitles in English containing material from patients who can recall the unpleasant delirium episode with detailed precision. A further DVD contains illustrative short films showing a patient during and after delirium. By using imaginative educational material (delier@amc.nl) as well as emphasising the high risk of complications of undetected and untreated delirium, it is now time to convince healthcare workers and policy makers of the need to implement programmes for screening, early prevention by multidisciplinary and multicomponent interventions, and provision of aftercare for delirium.

**Key points**

Delirium is highly frequent neuropsychiatric syndrome that can be precipitated by any somatic factor, which includes a variety of different illnesses, surgery or substance (medication) intoxication or withdrawal

Predisposing factors for delirium are increasing age and cognitive and functional impairment.

Delirium is independently associated with an increase in mortality, impaired physical and cognitive recovery, and increased hospital costs.

The current leading candidate for the final pathway of delirium is the neurotransmitter state of relative acetylcholine deficiency and dopamine excess, although an exaggerated inflammatory cascade seems to contribute.

Treatment of delirium consists of non-pharmacological measures, reversing the precipitating conditions, and judicious use of antipsychotics in severely agitated patients only.

**KEY WORDS:** Delirium, Diagnostic and Statistical Manual, DSM diagnosis, risk factors, dementia, pathophysiology, multifactorial prevention/treatment, antipsychotics, prognosis

**References**


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