Clinical Medicine 2014 Vol 14, No 2: 192–5

Delirium: a synthesis of current knowledge

Authors: Barbara C van Munster[A] and SE de Rooij[B]

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.[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.[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.[4–6] Given that it has been demonstrated that delirium can be prevented to a significant extent by a focussed approach, delirium can no longer be seen as an inevitable complication of illness and its incidence gives a helpful marker of quality of care.[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.[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.[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.

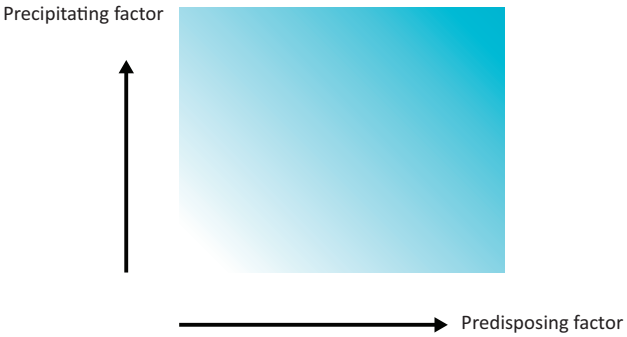

Fig 1. Relationship between predisposing and precipitating factors. Increasing darkness implicates a higher risk of delirium. Reproduced with permission from van Munster *et al* (2009).[12]

Risk factors

Previously, risk factors were divided into predisposing and precipitating factors by Inouye.[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.[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.[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.[14]

Recent literature splits risk factors into modifiable and non-modifiable, an approach that makes sense from the perspective

Authors: [A]medical specialist, Academic Medical Centre, Amsterdam and Gelre Hospitals, Apeldoorn, the Netherlands; [B]professor, Academic Medical Centre, Amsterdam, the Netherlands

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

DSM IV-R criteria	DSM 5 criteria
A Disturbance of consciousness with reduced attention	A Disturbance in attention
B Change in cognition or a new perceptual disturbance	C Change in *an additional cognitive domain*, not accounted for by another neurocognitive disorder
C Acute development and fluctuation over 1 day	B Acute development and fluctuation over a day and *not solely the result of another neurocognitive disorder*
	D *Disturbances in A and C must not be occurring in the context of a severely reduced level of arousal, such as coma*
D Caused by a somatic factor, medication intoxication or withdrawal	E Caused by a somatic factor, medication intoxication or withdrawal

DSM = *Diagnostic and Statistical Manual of Mental Disorders*. Changes in DSM-5 from DSM-IV shown in italics.

of prevention.[3] 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.[3] 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.[15] 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 intensive care unit, change of rooms during hospital admission, absence of help in orientation or vision and/or hearing aids.

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.[16] The current leading candidate for the final pathway is the neurotransmitter state 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.[17] Peripheral inflammation can activate the central nervous system (CNS) by several routes, including the circumventricular organs, vagal afferents and the brain endothelium.[18] These peripheral inflammatory signals also have severe deleterious effects on brain function when occuring in old age or in the presence of neurodegenerative disease.[19] In these circumstances, the cholinergic inhibition of primed microglia is reduced, leading to a exagerrated inflammatory cascade that could also account for the development of long-term cognitive impairment.[20]

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.[21–23] 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.[25,26] 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.[27]

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.[28,29] 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.[30] 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.[31] 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.[21,31] 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

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.[32] 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 (ie 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.[33]

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

1 Folstein MF, Bassett SS, Romanoski AJ, Nestadt G. The epidemiology of delirium in the community: the Eastern Baltimore Mental Health Survey. *Int Psychogeriatr* 1991;3:169–76.
2 Ely EW, Inouye SK, Bernard GR *et al.* Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–10.
3 Young J, Murthy L, Westby M *et al.* Diagnosis, prevention, and management of delirium: summary of NICE guidance. *BMJ* 2010;341:c3704.
4 Gross AL, Jones RN, Habtemariam DA *et al.* Delirium and long-term cognitive trajectory among persons with dementia. *Arch Intern Med* 2012;172:1324–31.
5 Witlox J, Eurelings LS, de Jonghe JF *et al.* Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304:443–51.
6 Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354: 1157–65.
7 Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev* 2007;CD005563.
8 Meagher D. Motor subtypes of delirium: past, present and future. *Int Rev Psychiatry* 2009;21:59–73.
9 Cole MG. Subsyndromal delirium in old age: conceptual and methodological issues. *Int Psychogeriatr* 2013;25:863–6.
10 Cole MG, Ciampi A, Belzile E, Zhong L. Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. *Age Ageing* 2009;38:19–26.
11 Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996;275:852–7.
12 van Munster BC, de Rooij SE, Korevaar JC. The role of genetics in delirium in the elderly patient. *Dement Geriatr Cogn Disord* 2009;28:187–95.
13 Webster R, Holroyd S. Prevalence of psychotic symptoms in delirium. *Psychosomatics* 2000;41:519–22.
14 Laurila JV, Laakkonen ML, Tilvis RS, Pitkala KH. Predisposing and precipitating factors for delirium in a frail geriatric population. *J Psychosom Res* 2008;65:249–54.
15 Carin-Levy G, Mead GE, Nicol K *et al.* Delirium in acute stroke: screening tools, incidence rates and predictors: a systematic review. *J Neurol* 2012;259:1590–9.
16 Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Semin Clin Neuropsychiatry* 2000;5:132–48.
17 Field RH, Gossen A, Cunningham C. Prior pathology in the basal forebrain cholinergic system predisposes to inflammation-induced working memory deficits: reconciling inflammatory and cholinergic hypotheses of delirium. *J Neurosci* 2012;32:6288–94.
18 Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9:46–56.
19 Cunningham C, Maclullich AM. At the extreme end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behaviour response. *Brain Behav Immun* 2013;28:1–13.
20 Van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet* 2010;375:773–5.
21 Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc* 2001;49:516–22.
22 Bo M, Martini B, Ruatta C *et al.* Geriatric ward hospitalization reduced incidence delirium among older medical inpatients. *Am J Geriatr Psychiatry* 2009;17:760–8.

23 Vidan MT, Sanchez E, Alonso M *et al.* An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. *J Am Geriatr Soc* 2009;57:2029–36.
24 Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007;CD005594.
25 Recupero PR, Rainey SE. Managing risk when considering the use of atypical antipsychotics for elderly patients with dementia-related psychosis. *J Psychiatr Pract* 2007;13:143–52.
26 Blom MT, Bardai A, van Munster BC *et al.* Differential changes in QTc duration during in–hospital haloperidol use. *PLOS ONE* 2011;6:e23728.
27 Lonergan E, Luxenberg J, Areosa SA, Wyller TB. Benzodiazepines for delirium. *Cochrane Database Syst Rev* 2009;CD006379.
28 de Jonghe A, Korevaar JC, van Munster BC, de Rooij SE. Effectiveness of melatonin treatment on circadian rhythm disturbances in dementia. Are there implications for delirium? A systematic review. *Int J Geriatr Psychiatry* 2010;25:1201–8.
29 Lammers M, Ahmed AI. Melatonin for sundown syndrome and delirium in dementia: is it effective? *J Am Geriatr Soc* 2013;61:1045–6.
30 McCaffrey R, Locsin R. The effect of music on pain and acute confusion in older adults undergoing hip and knee surgery. *Holist Nurs Pract* 2006;20:218–24.
31 Inouye SK, Bogardus ST, Jr, Charpentier PA *et al.* A multi-component intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340:669–76.
32 Schofield I. A small exploratory study of the reaction of older people to an episode of delirium. *J Adv Nurs* 1997;25:942–52.
33 Rahkonen T, Eloniemi-Sulkava U, Paanila S *et al.* Systematic intervention for supporting community care of elderly people after a delirium episode. *Int Psychogeriatr* 2001;13:37–49.

Address for correspondence: Dr BC van Munster, Department of Internal Medicine, Academic Medical Centre, PO Box 22660, 1100 DD Amsterdam, the Netherlands. Email: b.c.vanmunster@amc.uva.nl