

Geriatric Giants Lecture Series

DELIRIUM

Darryl Rolfson, MD, FRCPC

Division of Geriatric Medicine
Department of Medicine
University of Alberta

Division of Care of the Elderly
Department of Family Medicine
University of Alberta

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Picture a student intern attempting to obtain a medical history from a quiet yet delirious older patient. The interview is nearly abandoned when the patient falls asleep mid-conversation. The student intern perseveres but gradually become frustrated when the senior seems inattentive, speaks incoherently and constantly changes the subject.

Such a scene, when viewed from a distance, takes on the melodrama of a Vaudevillian play. The student intern is the “hero”; approaching the patient “in distress” with the time honored medical history. Lurking in the background and seen only by the audience is the villain – in this case, *DELIRIUM* (Boo! Hiss!). The audience, aware of the villain, is warning him, “Look behind you!” Our hero valiantly perseveres, asking more questions, re-examining nervous system, and prescribing more sedatives. Yet the delirium itself remains unnoticed, while the student intern becomes increasingly frustrated with an assessment that is going nowhere. Ironically, until the delirium is truly recognized, and its causes carefully elucidated, the condition will remain, and adverse consequences will become increasingly certain.

This may seem to be an unfair comparison. Yet as will be reviewed, delirium is common, frequently overlooked by physicians, and deadly. Even worse, it is often iatrogenic in its origins. Delirium in a frail older person defies the traditional ‘single disease entity’ model of medicine (see the frailty and illness presentation lecture), and is the prototype for the acute geriatric syndromes. As such, the themes that arise from its review illuminate the approach to similar syndromes such as falls, immobility, acute functional decline, acute manifestations of nutritional deficiency and acute urinary incontinence. These syndromes are also common and under-recognized.

1. Delirium – the nature of the beast

Terms such as ‘organic brain syndrome’, ‘metabolic encephalopathy’, acute confusional state’ and ‘toxic psychosis’ are sometimes used to describe delirium. The ancient Greeks seemed to recognize the hyperactive and hypoactive manifestations of delirium when they described respectively, ‘phrenitis’ (frenzy) and ‘lethargus’ (lethargy). Perhaps Celcus had it right when he first coined the term delirium: ‘de lira’ meaning ‘off the path’. With every new iteration, the authors of the diagnostic and statistical manual (DSM) criteria tend to reshape their terminology. However, the core features of the syndrome remain as the standard, as can be seen in the DSM IV-TR Criteria for delirium (1). All four criteria must be met:

- A disturbance of *consciousness*
- A *change* in cognition

- The disturbance *develops over a short period of time and tends to fluctuate*.
 - There is evidence that the disturbance results from a medical condition, substance intoxication or substance withdrawal
- (a) **A disturbance of consciousness.** Delirium is primarily a disorder of consciousness. Even individuals with significant cognitive impairment may retain the ability to attend to their environment and maintain their focus. An altered sensorium can be particularly difficult to detect on the first encounter with a patient. The patient may be inappropriately drowsy. If awake, the individual may be inattentive or easily distracted by other sensory stimuli. The stream of thought may appear to be very disorganized. Truly, a delirious person will demonstrate cognitive ability, and yet will quickly be derailed – or off the path (remember Celcus?)
- (b) **A change in cognition.** There are very few entities in old age that will manifest as a sudden decline in cognitive performance. When such a history is obtained through family or caregivers, delirium must be suspected until otherwise proven. Sudden changes in cognition may also be seen in a stroke. This may be subtle as in the ‘step-down’ of vascular dementia. However, even then, delirium commonly co-exists in the acute stage.
- (c) **Short period of onset and temporal fluctuation.** Delirium classically fluctuates in its severity and in its nature over the day. The *severity* of the delirium may fluctuate. For example, it may be less obvious in the morning when physicians are rounding and be most pronounced in the evening (sundowning) when only nursing staff are present. The fluctuation in severity may even be noticed on an ‘hour to hour’ basis. Alternatively the *nature* of the delirium may alternate between a quiet, hypoactive delirium and an agitated, hyperactive delirium. Low-grade fluctuation in cognitive performance is sometimes seen in an isolated dementia as well. However, there will not be a short period of onset, nor a true disturbance of consciousness.
- (d) **Underlying etiology.** Usually delirium can be attributed to an acute medical illness, an adverse drug reaction, substance withdrawal, or some combination of these. Contributing variables including environmental influences, pain and sensory impairments are unmistakable, but these are not currently a necessary part of the DSM IV classification scheme. Prompt resolution of the confusional state when all of the potential contributors have been addressed further confirms the delirium.

A common dilemma in assessing the confused patient is distinguishing delirium from dementia. In both entities, there may be global cognitive dysfunction in such domains as memory, receptive language, praxis, abstract thought, visuospatial abilities and judgement. Neurobehavioral derangements are also seen in both, including hallucinations, delusions, motor agitation, physical

aggression, and hypoactivity. However, even when delirium is superimposed on a dementia, the core features of the delirium as described above are crucial to the diagnosis.

An analogy that may help distinguish delirium from dementia is the landscape analogy. Delirium without dementia is like a view of an intact landscape with a fog intermittently obscuring the rich details from view. In fact, a person experiencing delirium may describe being in and out of “a fog”. Dementia is like an impoverished landscape that is plainly in view. The pattern of dilapidation may reflect different types of dementia.

The retention of some insight and the acute onset of delirium may lead a delirious person to perceive that “something isn’t right”. An observant clinician may see this in their facial expressions or in their body language. The sense that something is not right may prompt the patient to attempt to make it “right”, manifest to caregivers as agitation or excessive psychomotor activity. Those who can retain a recollection may say that delirium is not unlike the momentary panic that any one of us might experience after suddenly awakening in an unfamiliar environment. The difference, of course, is that the feeling of strangeness in delirium does not quickly resolve after reorientation.

2. Why should we care about delirium?

- (a) **Delirium is common.** The prevalence of delirium in seniors at the time of admission to hospital is estimated to be 10 to 22%. Thereafter, the incidence during hospital admission is 7 to 31% on general medicine, 33% for cardiac surgery and as much as 40 to 60% on orthopedic units.
- (b) **Delirium is under-recognized.** Despite excellent diagnostic criteria, prospective studies consistently show a failure of clinicians to recognize delirium. For example, Gustafson et al followed a prospective cohort of elderly hip fracture patients (n=111) and found an incidence of delirium of 62% (4). When present, delirium was poorly recognized by nurses (39% of delirious patients) and physicians (22% of delirious patients)

Why do we as physicians do such a poor job of recognizing this condition? Some reasons may be the following:

- (i) **Delirium is misread** by hospital staff as a dementia or simply attributed to age. The hospital encounter provides only a snapshot view of the patient. An appreciation of their baseline cognitive status would allow the current state of confusion to take on new meaning.
- (ii) **Delirium fluctuates** and will be missed if the patient is assessed on the basis of a single encounter during a lucid interval.

- (iii) **Hypoactive subtypes are common in the elderly.** About half of the time, the manifestation of delirium is hypoactive, which is not usually alarming to caregivers.
 - (iv) **Delirium is not taken seriously.** Unless delirium is appreciated to be a medical urgency, it may not be taken as seriously as it should be, and thus not recognized for what it is. In the frail older person, classic physical and biochemical signs of acute illness may be lacking. Yet, considering its significant mortality, morbidity, and functional impact, delirium should be dealt with as urgently as a new WBC count of 30, a sodium of 160, severe hypoxia, or an acetaminophen overdose.
- (c) ***Delirium is often iatrogenic.*** As will be seen below, delirium is strongly associated with the use of certain medications. Even the process of hospital care can contribute to its development. A landmark prevention trial by Inouye et al (3) recently showed a statistically significant absolute risk reduction of 5.1% in an elderly cohort who were prospectively matched to participate in standard “process of care” protocols. These standardised protocols addressed predisposing risk factors including cognitive impairment, sleep deprivation, immobility, visual and hearing impairment, and dehydration. Process of care issues which may set the stage for delirium and its consequences are not restricted to iatrogenesis alone. Other system wide variables which must also be addressed include skills in the recognition of delirium, attitudes toward the care of the elderly, the rapid pace and technological focus of hospital care, and reductions in skilled nursing staff (4).
- (d) ***Delirium is costly.*** Considering that a large number of acute medical conditions can both cause delirium and cause death, an association between delirium and mortality is not surprising. This indeed has been recognized at least for a quarter century. What is remarkable is that in multivariate analysis (in which all potential factors associated with the outcome are considered), there is an independent association between delirium and death. Delirium is also independently associated with a prolongation of the hospital stay, placement in institutional setting, and a decline in the ability to perform activities of daily living, and subsequent dementia.

3. An approach to diagnosis

The diagnosis of delirium can be quite elusive. However, experience has shown that the following approach will greatly increase the identification of delirium and its causes:

- i. Anticipate it.
- ii. Obtain relevant and reliable information
- iii. Interview and conduct objective testing
- iv. Satisfy criteria for delirium
- v. Investigate for the precipitating cause

- a. **Anticipate it.** The setting itself should be the first trigger. Any hospitalized older person will be at risk – especially those who happen to be on cardiac surgical and orthopedic units. There will be pre-existing characteristics of the patient that also will raise the suspicion. Demographic and social factors, which are independently associated, include advancing age and male gender. Delirious patients are more likely to have been social isolated or to have lived in an institutional setting. Visual and hearing impairment make delirium significantly more likely. Cognitive impairment, particularly dementia, and a history of depression are important in increasing the vulnerability to delirious episodes. Other important predisposing variables include functional dependency, immobility, and malnutrition. Alcohol and benzodiazepine dependency set the table for delirium. The burden of medical comorbid illness is an important consideration. In particular, a history of stroke, Parkinson's disease, Azotemia and liver dysfunction should prompt the clinician to consider delirium in the acute setting.
- b. **Obtain relevant and reliable information.** Following a brief review of the health record, attempts to obtain information should begin with the patient themselves. Open-ended questions should reveal the whether the patient retains insight into their health history. In a sense then, the mental status exam really begins with the history. If it is obvious that the information is unreliable, the remainder of the clinical encounter should focus on the physical exam and the mental status exam (see below). Relevant and reliable information should be sought from two sources: nursing staff and family members. Nursing staff (and their notes) will provide a view of the patient over the day, thus identifying the fluctuating course and the pattern of cognition and behavior. The collateral history obtained from family and friends will be helpful in establishing the cognitive baseline.
- c. **Interview and objective testing.** For the potentially delirious individual, the mental status exam begins in the moment you step into the patient's room. Does the patient notice your arrival? Can you 'engage' the patient and is eye contact maintained? Does the patient appear to be peaceful and in control or is there a sense that "something is not right"? Make note of motor activity. Are the bedsheets and hospital clothing in disarray? Continue to consider the core features of delirium as you introduce yourself, develop rapport, and proceed with the history. Keep in mind that problems with communication with the patient may be related to visual or hearing impairment. Ensure that the proper aids are in place and the room is quiet and well lit. You may already have obtained objective observations by family or nursing staff as a standard for comparison. If the reliability of the history remains questionable, it will be worthwhile to shift to the mental status exam early in the visit in order to rule out delirium.
 - (i) The **Folstein Mini Mental Status Exam** (5) is perhaps the best known of bedside cognitive instruments. It tests attention and

calculation in addition to orientation, registration, recall, language, and construction. Although it was validated simply for “cognitive impairment” (defined as a score of less than 24/30), it is commonly used in a serial fashion to monitor the development and resolution of delirium. The instrument has not been validated for the presence or severity of any diagnostic entity (including delirium).

- (ii) The **Clock test** was originally used to examine constructional apraxia, however its use as a general cognitive screening tool has become popular over the past ten years. The task is complex, requiring other cognitive skills such as attention and concentration. It has been validated for screening in Alzheimer’s disease, but so far not for delirium. An abnormal clock does appear to be useful in predicting postoperative delirium (6). While it is a very practical bedside tool, a generally accepted scoring system is still lacking, making its interpretation problematic.
- (iii) **Simple Bedside tests of attention.** Because inattention is central to the clinical diagnosis of delirium, those tests, which target this cognitive domain, are often found to be useful. Tests which are simple, minimizing the need for abstract thought or complex language allow applicability both to individuals with varied educational and cultural backgrounds and to persons with other preexisting cognitive deficits. The **Vigilance A test** is done by the examiner slowly reciting a series of random letters, among which the letter A appears at greater than random frequency. The subject is required to raise their hand whenever the examiner says the letter A. More than two errors (omission or commission) in 60 letters constitute an abnormal test. **Digit span** is performed by asking a subject to repeat a series of random digits. The examiner starts with a short series (two or three digits separated by one second intervals) and proceeds with each successful repetition by increasing the length of the digit span by one. Failure to correctly repeat five digits is considered abnormal. **Serial subtractions** is another simple bedside test which is done by instructing the subject to count back from a number in predetermined intervals until they reach zero. Generally, the patient would be asked to count back from 40 by fours (Less challenging tests would be to count back from 20 by twos or from 10 by ones). Errors such as deletions, repetitions, or abandonment of the test would not be met with “coaching” by the examiner. The sensitivity of all three tests for inattention or distractibility can be enhanced by “turning up the background noise”: examining in a noisy setting such as an emergency room or concurrent tapping of a pencil by the examiner. Digit span and Vigilance A test have been cross validated (7).

- d. **Satisfy criteria for delirium.** The DSM criteria for delirium have been previously described, and include a disturbance of consciousness, an acute

change in cognition with daytime fluctuations and evidence that the disturbance results from a medical condition, substance intoxication or substance withdrawal. A useful algorithm-based instrument for the diagnosis is the **Confusion Assessment Method** (CAM) (8). When used by individuals, who also have the ability to diagnose delirium, the CAM is highly sensitive and specific. Poor sensitivity of the CAM has also been observed in individuals who are not trained to diagnose delirium (9). The ideal time to apply the CAM criteria would be **after** collateral sources have been sufficiently explored and the patient has been adequately interviewed. The CAM criteria can be committed to memory using the acronym, 'AIDS':

- Acute and Fluctuating Course
- Inattention
- Disorganized Thinking
- Sensorium is altered.

e. **Investigate for the precipitating cause.** When delirium is confirmed, the job has only just begun. Considering that the management of delirium is first and foremost to 'treat the underlying cause', a sometimes exhaustive search then ensues to identify 'the cause'. In fact, finding the causes of a delirious state becomes the central activity of a health care provider who is interested in its resolution. Delirium causation is best understood in the multifactorial model presented in the lecture on frailty and disease presentation. The pattern of predisposing factors will have already been anticipated. The most likely precipitating causes will largely emerge from the profile of frailty. For example, in a young otherwise well individual who presents with delirium, there is likely to be a single, severe stressor such as overwhelming sepsis or a serious central nervous system condition. In the frail elderly with multiple underlying comorbidities, however, the causes tend to be multifactorial, and the relative physiologic stress required to induce the delirium would seem to be less. In order of importance, these include medications, medications, medications, infectious causes, metabolic causes, and cardiopulmonary causes. Contributing factors may include pain, retention syndromes, and environmental causes. Neurologic causes are also a consideration after these have been ruled out.

- (i) **Medications.** Review all of the *prescription* medications, particularly those that may have been changed recently. The 'usual suspects' include narcotics, anticholinergic drugs, benzodiazepines, neuroleptics, antidepressants and anti-parkinsonian drugs. Drugs that are of a moderate risk but commonly used are therefore sometimes implicated. These include most antibiotics, H2 antagonists, Beta Blockers, and NSAIDs.
- (ii) **Medications.** Review all *over the counter* medications.
- (iii) **Medications.** Consider those medications that come in '26 oz bottles' and other substances that may be abused. Consider both intoxication and withdrawal of these substances.

- (iv) **Infectious Causes.** The most common infections will also be the most common causes of delirium – ensure that the urinary tract and chest have been carefully examined and investigated. All body surfaces should be exposed to identify soft tissue sources. Remember that infections can hide in deep abscess cavities, retroperitoneal spaces, the rectum and the ear, nose, and throat. A complete blood count, differential, urinalysis and chest X-ray should be ordered early. These may be supplemented by urine, blood, or sputum cultures. Do not rely too heavily on the absence of fever or leukocytosis in a frail older person. Bacteruria in a delirious person who is unable to communicate their symptoms should be presumed to be symptomatic. In a persistent, unexplained delirium, and especially in a suspicious clinical setting, a lumbar puncture is an important consideration.
- (v) **Metabolic Causes.** Considering the sometimes bland manifestations of these life-threatening conditions in immobile and delirious seniors, there must be vigilance in their search. In a diabetic, hyperglycemic non-ketotic coma, ketoacidosis and hypoglycemia must be considered and a simple chemstrip is a sensible early measure. Hypercalcemia in the setting of malignancy or hyperparathyroidism may manifest as delirium. Myxedema and thyrotoxicosis are important causes of delirium, which must be identified and treated. Adrenal insufficiency may also may evolve slowly and remain unrecognised in a sessile, delirious senior. Hepatic failure and renal failure will cause delirium, primarily when fulminant or acute in evolution. Disorders of water balance are often reflected in the serum sodium levels. There is an independent association between delirium and ‘sodium abnormalities’, hyponatremia and hypokalemia, and dehydration. Hyponatremia is the most common electrolyte abnormality in the hospitalised senior. Numerous causes are possible and its work-up and appropriate management is thus crucial in a delirious individual. Hyponatremia in a confused older person is particularly alarming considering the associated mortality. When increased fluid and salt intake do not compensate renal or extra renal losses of water, a vicious spiral of immobility and delirium may further exacerbate the situation. These electrolyte disturbances may also be coupled with endocrinological abnormalities sited above. Hypokalemia, hyperkalemia, and acid base disorders can also cause delirium and death. Without clinical clues, a basic work-up should include serum electrolytes, glucose, creatinine, calcium and thyroid stimulating hormone (TSH). If necessary, further probing may also include liver function tests and a serum cortisol followed by the cosyntropin test if there is clinical and biochemical suspicion of adrenal insufficiency.

- (vi) **Cardiopulmonary Causes.** Considering the potential for cerebral hypoxemia, hypoperfusion states and pulmonary compromise would seem to be an obvious consideration in an unwell delirious individual. Yet in the work-up of such an individual, it is surprising how often this category of potential etiology is neglected. An independent association with delirium has been demonstrated for hypoxemia, shock, and a postoperative hematocrit less than 30%. Exacerbations of chronic obstructive lung disease and congestive heart failure undoubtedly can stimulate delirium in a susceptible individual. Delirium is witnessed in the context of myocardial infarction and pulmonary embolism. A careful physical examination may be the only clue that suggests a cardiopulmonary source of the delirium. This should be followed by appropriate radiological or electrocardiographic investigations. Non-resolving delirium often can be reversed with scrupulous attention to these underlying precipitants.
- (vii) **Other Contributing causes.** There are other factors that only rarely will be the sole explanation for delirium. Still, these factors may perpetuate the delirium and thus these must be addressed. Pain, psychological stress, sleep deprivation, urinary retention and fecal retention can amplify the severity of delirium. Potential extrinsic variables are numerous, and include immobilisation and immobility, physical restraint use, bladder catheter use, sensory overload (noise, frequent room changes, “iatrogenic events” and intensive care unit treatment,) and sensory deprivation (the lack of “orienting objects”, “low social interactions”, lack of windows, unfamiliar environments).
- (viii) **Neurologic Causes.** A subdural hematoma or new stroke may also occur in the absence of obvious focal neurological signs. Anticipation of such possibilities should rise given a history of confusion and falls. One must also be constantly aware of the potential for a cerebral haemorrhage, a primary tumour, brain metastasis, an abscess, meningitis, encephalitis, and petit mal or partial complex seizures. These too may occur in the absence of clues on physical examination. It is for this reason that further investigations for these entities should proceed both in the presence of historical or examination clues and when there is persistence of delirium after ruling out common causes. Practices will vary depending on the composition of the referral population and the comfort level of the clinician. These investigations may include but not be limited to a CBC and differential, blood cultures, neuroimaging, an electroencephalogram and a lumbar puncture.

4. Management of delirium

The management of delirium is specific, supportive and sometimes sedative.

- a. **Specific.** The treatment of delirium hinges on the identification and treatment of the specific underlying causes. This may require active medical or surgical treatment or the discontinuation of drugs. In over 90% of cases, causes can be found and treatment will lead to resolution of the delirium. A good rule of thumb is that the delirium will take as long to resolve as it did to develop. Therefore, the delirium may take days to resolve even after the causes have been treated. During this time, it will be reassuring if the delirious episodes become less severe and shorter in duration, while the lucid intervals progressively lengthen.
- b. **Supportive.** The goal of supportive care is to make the patient's external environment as familiar as possible. Common sense should guide caregivers to ensure that the patient benefits from the right aids, the right physical environment, and the right approach.
 - (i) **The right aids.** All who interact with the patient should first ensure that proper hearing & visual devices are in place to optimize communication. The patient should be in the upright posture as much as possible.
 - (ii) **The right physical environment:** Adequate light is crucial. A large window may aid in restoring normal diurnal patterns. The presence of a good clock and calendar well in view of the patient coupled by the placement of familiar objects, photographs and art can be helpful. Hospital noises should be minimized and catheters and other devices removed if possible. Supervision for meals is advised. Supervised ambulation can also reinforce the patient's sense of familiarity with their surroundings. This approach generally obviates the need for physical restraints.
 - (iii) **The right approach:** A calm, non-threatening approach by familiar visitors and regular staff is ideal. This is not always possible. However, if family members can be particularly helpful in this regard. Social isolation can be particularly troublesome for the delirious patient who is also on isolation precautions. An extra effort to maintain contact will be well worth it.
- c. **Sedative.** A sedative (neuroleptic or benzodiazepine) is unlikely to lead to resolution of delirium without the treatment of the underlying cause. However, as a temporary measure in the context of an agitated patient, a sedative can be considered. The primary reason to use a sedative is to convert hyperactive symptoms to hypoactive symptoms.

When there are psychotic symptoms such as delusions and hallucinations, an antipsychotic may be the sedative of choice. Haloperidol (Haldol) is a high potency neuroleptic, and the first line agent regardless of the route (10). Newer atypical neuroleptics such as risperidone (Risperdal), olanzapine

(Zyprexa), and quetiapine (Seroquel) offer an attractive but less proven alternative to haloperidol and loxepine, especially if side effects are anticipated or if the drug may be used for a longer period of time. Any neuroleptic can both worsen delirium and cause extrapyramidal symptoms.

Benzodiazepines do have a place in the sedative management of delirium that results from alcohol or benzodiazepine withdrawal.

5. Prevention of Delirium

Considering the scope and cost of delirium, there is emerging interest in its prevention, especially in hospital settings. A systematic review in 1996 found a paucity of such studies (11). One case-matching study (3) has applied a multi-component intervention to this end. The investigators applied six standardized protocols to managing specific risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration. This resulted in a significant reduction in the number and duration of episodes of delirium in hospitalized older patients (one delirious patient prevented for every 19 patients who received the intervention). Considering the cost of delirium, the intervention was viewed as cost-neutral. Notably, this intervention did not target two key preventable precipitants of delirium in the elderly, drugs and infections.

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