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A Review of the Etiology Delirium

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1. Introduction

Delirium, also called as organic brain syndrome, acute brain syndrome, acute brain failure, acute confusional episode and reversible or masked dementia, as a concept, stretches back to the age of Hypocrates (Burns et al., 2004). Delirium is described as a condition characterized by a disturbance of consciousness with reduced ability to focus, sustain, or shift attention according to the Diagnostic and Statistical Classification of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000). Also, delirium involves 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 preexisting, established, or evolving dementia (American Psychiatric Association, 2000). In addition to these, impairment in the brain's ability to integrate perceptions correctly, coupled with memory deficits and confusion may result in psychotic symptoms in delirium. Hallucinations (especially visual and tactile), delusions, paranoia, illusions, and bizarre behavior are the commonly encountered psychotic symptoms in delirium (Leigh, 2008).

Delirium is associated with longer hospital stay, poorer functional outcome, and cognitive decline in addition to an elevated morbidity and mortality. Despite these adverse outcomes, delirium recognition rates are low (12–43%) and its management remains inadequate in up to 80% of patients (Morrison et al., 2003). These findings suggest lack of preventive and screening activities, missed diagnoses, and inappropriate management of diagnosed delirium (Michaud et al., 2007).

2. Epidemiology

2.1 Prevalence

The prevalence of delirium varies with the population that is being studied (Fong et al., 2009). Delirium is a relatively common disorder, especially in older people with physical illness (Saxena & Lawley, 2009). Community rates of delirium are reported to vary from 0.4% to 2% (Saxena & Lawley, 2009, Fong et al., 2009). In general hospital setting prevalence of delirium has been reported to range from 11% to 33% on admission (Lindesay et al., 2002) and its incidence during hospital stay ranges between 3% and 56% (Inouye, 2006; Michaud L et al., 2007).

Delirium rates depend on the setting in which the patient belong; for example, delirium prevalence has been reported to be between 7-10% in emergency department, whereas it has been reported to be as high as 33% in the orthopedic surgery patients (Samuels & Neugroschl, 2005). Postoperative delirium is reported to be in 15% to 62% of elderly patients (Saxena & Lawley, 2009, Fong et al., 2009). Higher rates of delirium have been reported in elderly patients in intensive care units (ICU), which ranges from 70% to 87% (Saxena & Lawley, 2009, Fong et al., 2009).

Children are also at risk of delirium. There is a paucity of data on the rates of delirium in children, but delirium was reported to be seen in 10 to 40 percent of preschool children during emergence from anesthesia. Children with severe burns and fever are at risk for delirium (Saxena & Lawley, 2009).

3. Etiology

Delirium is divided into subtypes according to the etiological factors. When 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, it is called as *Delirium due to a general medical condition*. When the symptoms of delirium are due to substance intoxication, it is called as *Substance intoxication delirium*. When the delirium is due to substance withdrawal, it is called as *Substance withdrawal delirium*. When there is evidence from the history, physical examination, or laboratory findings that the delirium has more than one etiology, it is called as *Delirium due to multiple etiologies*. Delirium that is of unclear etiology is called as *Delirium not otherwise specified* (American Psychiatric Association, 2000).

Delirium usually has a multifactorial etiology. It has been reported that 90% of patients with delirium had three to four identifiable etiologic factors, 27% had two factors, and only 16% had one identifiable etiologic factor (Camus et al., 2000). The etiology of delirium is complex and multifactorial, with the interaction of precipitating factors (acute insults) on a vulnerable patient with predisposing conditions (Inouye, 1999).

3.1 Predisposing factors

The predisposing factors are those that place patients vulnerable to develop delirium. Older age, neurological disorders, male sex, sensory impairment, depression, functional dependence, immobility, hip fracture, dehydration, alcoholism, severity of physical illness, stroke, metabolic abnormalities are among the predisposing factors that increase an individual's vulnerability to delirium (Inouye, 1999; Burns et al., 2004; Fong et al., 2009; Staus, 2011). The National Clinical Guideline Center (in the UK) has published a data synthesis on this topic commissioned by the National Institute for Health and Clinical Excellence (NICE). In this analysis, the risk factors for delirium were reported as age 65 years or older, cognitive impairment (past or present) and/or dementia, hip fracture on admission, severe illness (a clinical condition that is deteriorating or is at risk of deterioration) (National Clinical Guideline Center).

3.1.1 Age

One of the most important predisposing factors is age (Inouye, 1999). Both the geriatric and pediatric populations are at risk of developing delirium (Dulcan, 2010). The elderly are

more vulnerable to delirium because of the age-related loss of cholinergic reserve that is necessary for memory, learning, attention, and wakefulness (MacLulich et al., 2008).

Among this age group, one of the most common risk factors for delirium is dementia, with two-thirds of elderly cases of delirium having comorbid dementia (Fong et al., 2009). Delirium and dementia are both associated with cholinergic deficiency (Hshieh et al., 2008) and decreased cerebral blood flow or metabolism (Fong et al., 2006, Yokota et al., 2003); these common properties might explain the relationship between these two conditions (Eikelenboom and Hoogendijk, 1999; Fong et al., 2009).

As mentioned above, the main mechanism that predisposes elderly to delirium is diminished cholinergic reserve; on the other extremes of age are children who are also prone to delirium because of the immature and evolving structural brain development (Williams, 2007). According to the study of Leentijens et al., 2008, etiological factors differed among pediatric, adult and geriatric populations; for children neurological, respiratory and circulatory disorders were among the most important causes of delirium (with ratios of 39%, %26, %17 in order), whereas for adults the most common factors were medication intoxication or withdrawal (24%), brain metastases/CNS neoplasms (24%) and metabolic and endocrine causes(20%), for elderly patients metabolic and endocrine causes (26%), systemic effects of a neoplasm (19%), medication intoxication or withdrawal (19%) were most important factors (Leentijens et al., 2008).

3.1.2 Neurological disorders

Dementia is a major predisposing factor for delirium, a meta-analysis suggesting a relative risk of 5.2 (Elie et al., 1998). Fick et al. reported that approximately 45% of patients with dementia develop delirium during hospitalization (2002). Elderly patients with dementia are at higher risk for developing delirium not only because they have the usual age-related decrease in acetylcholine described previously, but also have a focal loss of acetylcholine due to death of the cholinergic cells in the nucleus basalis of Meynert as a result of the disease process (Tune & Egeli, 1999).

In a study that included patients over the age of 65 years admitted to hospital with a fractured neck of femur, cognitive impairment which was measured by the Mini-Mental State Examination (MMSE), has been found to be the most significant predisposing factor for the development of delirium (Freter et al., 2005).

Other neurological causes are cerebrovascular diseases (thrombosis, embolism, arteritis, hemorrhage, hypertensive encephalopathy), degenerative disorders (multiple sclerosis), epilepsy, head trauma, space-occupying lesions (tumor, subdural hematoma, abscess, aneurysm) and encephalitis (Michaud et al., 2007; Fong et al., 2009).

3.1.3 Hip fracture

Hip fracture patients are at increased risk of delirium because of the trauma associated with the injury and the rapid progression to hospitalization and surgery, in addition to the pain and loss of function (Schor et al., 1992; Williams et al., 1985). Delirium has been reported to be seen in 20%–40% of patients with hip fracture at the time of hospital admission (Magaziner et al., 1989; Gustafson et al., 1991; Marcantonio et al., 2002).

The most common of delirium in hip fracture patients were reported as drugs that have central nervous system effects, infections, fluid-electrolyte disturbances, metabolic/endocrine disturbances, intracranial processes, cardiopulmonary compromise and/or drug withdrawal and sensory/environmental causes (Brauer et al., 2000).

3.1.4 Severe, traumatic or systematic illnesses

Medical comorbidities such as burns (Palmu, 2011), cancer (Bond et al., 2011), cardiovascular disease (Branco et al., 2011), and alcoholism (Pompei et al., 1994) are among the predisposing factors for delirium. Sensory impairments like visual impairment and functional dependence also predispose individuals to delirium (Burns et al., 2004). In a study investigating a multifactorial model of delirium etiology, a predictive model was formed and 4 predisposing factors were identified for delirium: vision impairment, severe illness, cognitive impairment and BUN/creatinine ratio of ≥ 18 (Inouye, 1999).

Having a severe illness and staying in intensive care unit are also predisposing factors for delirium. Delirium has been reported in up to 80% of critically ill patients (Ouimet et al., 2007). Delirium is an independent predictor of adverse intensive care unit outcomes, including increased risk of death, longer hospital stay, and higher costs (Ely et al., 2004; Milbrandt et al., 2004; Thomason et al., 2005).

3.1.5 Male gender

Male gender was found to be a risk factor in some of the studies of delirium (Williams-Russo et al., 1992; Fisher & Flowerdew, 1995; Kolbeinsson & Jonsson, 1993; Schor et al., 1992; Edlund et al., 2001). In the meta-analysis of Elie et al., a statistically significant relative risk of 1.9 was found for the male gender (1998). In a study that investigated the differences between preoperative and postoperative delirium regarding predisposing, precipitating factors and outcome in older patients admitted to hospital with femoral neck fractures, it was found that the men with femoral neck fractures were in poorer health than the women, except that more female patients had hypertension and were treated with diuretics (Edlund et al., 2001). In the same study, male patients were reported to suffer more postoperative complications and have higher long-term mortality (Edlund et al., 2001). These factors might have contributed to the increased risk of delirium in men.

Another factor contributing to the increased risk of delirium in men might be reluctance of men to consult a doctor. Men with health problems were found to be more likely than women to have had no recent contact with a doctor regardless of income or ethnicity (Courtenay, 2000). This reluctance means that men often do not seek help until a disease has progressed (Banks, 2001).

3.1.6 Depression

Depression has been reported to be a predisposing factor for delirium in the elderly (Elie et al., 1998) and in non-cardiac surgical patients (Dasgupta and Dumbrell, 2006). The reduced functional connectivity in the human brain which is associated with depression (Anand et al., 2005) was hypothesized to be one of the mechanisms that predispose depressive patients to delirium (Sanders, 2011). On the other hand, the authors of the data synthesis commissioned by the National Institute for Health and Clinical Excellence (NICE) reported

uncertainty for depression as a precipitating factor for delirium (National Clinical Guideline Center; Steiner, 2011).

3.2. Precipitating factors

Precipitating factors are the acute insults that trigger the mechanisms resulting in delirium (Fong et al., 2009; Inouye, 1999). Factors that have been reported to precipitate delirium are: anemia (Joosten et al., 2006), hypoxaemia (Kazmierski et al., 2010), Intensive Care Unit admission (Branco et al., 2011), electrolyte abnormalities (Korevaar et al., 2005), sleep deprivation (Weinhouse et al., 2009), pain, bladder catheter use, drugs and surgery (Burns et al., 2004). Biochemical abnormalities such as hyponatremia and hypokalemia and hyperuricemia and low body mass index and sensory impairment reflects the severity of the underlying precipitating cause of delirium (Elie et al., 1998; Mussi et al., 1999).

Inouye and Charpentier performed a study to establish a predictive model for development of delirium and identified 5 independent precipitating factors for delirium in the elderly: use of physical restraints, malnutrition, more than 3 medications added, use of bladder catheter and any iatrogenic event (Inouye & Charpentier, 1996). Among the predisposing factors, surgery and drugs will be discussed in this section.

3.2.1 Surgery

The incidence of post-operative delirium ranges from 5% to 15% (Deiner & Silverstein, 2009). Certain high-risk groups have increased rates of delirium. Delirium has been reported in 16.3% after cardiac surgery (Kazmierski et al., 2010). Rates as high as 30.2% after hip surgery (Lee et al., 2011) and 50% have been reported in elderly patients (Inouye et al., 1993; Dasgupta & Dumbrell, 2006). Factors that increase the risk of delirium in surgical patients include electrolyte disturbances, increased age, dementia, low cardiac output, perioperative hypotension, postoperative hypoxia, and use of anticholinergic drugs. (Michaud et al., 2007; Norkiene et al., 2007). Pandharipande et al. found that 70% of the combined surgical and trauma ICU patients had at least one episode of delirium (Pandharipande et al., 2007).

3.2.2 Drugs

Delirium is characterised by a global cerebral dysfunction resulting in a generalized reduction in cerebral oxidative metabolism and an imbalance of several neurotransmitters in the brain. Any drug that interferes with these neurotransmitter systems or with the supply or use of substrates for metabolism of the central nervous system can cause delirium (Gray et al., 1999; Moore & O'Keeffe, 1999; Nayeem & O'Keeffe, 2003). For a drug to be clearly implicated as an etiological factor in delirium, the administration of the drug should precede the onset of symptoms of delirium within a short time duration and withdrawal of the drug should result in a return to baseline cognitive functioning (Moore & O'Keeffe, 1999).

3.2.2.1 Anticholinergic drugs

The causal association of drugs to delirium is most clear for anticholinergic drugs with muscarine receptor affinity (White et al., 2007). Antihistaminics, antipsychotics, tricyclic antidepressants, digoxin, frusemide, isosorbide dinitrate, warfarin, dipyrindamole, codeine,

and captopril are among the mostly used drugs that have primary or secondary anticholinergic effects contributing to risk of delirium (Burns, 2004). Many commonly used drugs in the elderly, that are the principal treatments of clinical conditions, such as urinary incontinence and cardiovascular disease, have anticholinergic properties (Scheife & Takeda, 2005; Uusvaara et al., 2011). Older patients and those with mental illness are particularly vulnerable to the adverse neuropsychiatric effects of anticholinergics as they may already have cognitive impairment (Gerretsen & Pollock, 2011).

3.2.2.2 Opioids

Delirium has been reported to be associated with opioid use (Gray et al., 1999, Brouquet, 2010). The association of delirium with opioids is dose-related (Burkhart et al., 2010). Persistent delirium has been reported to be associated with use of opioids at doses greater than 54mg/day (Pisani et al., 2010). On the other hand, there are studies reporting no association between opioid use and delirium (Pandharipande et al., 2006; Pisani et al., 2007). In a systemic review which aimed to determine medications to avoid in people at risk of delirium, it was concluded that, although use of opioids should be prescribed with caution in people at risk of delirium, as untreated severe pain can itself trigger delirium, this caution should be tempered (Clegg & Young, 2011).

3.2.2.3 Antidepressants

All tricyclic antidepressants have an anticholinergic effect, with amitriptyline having the strongest and nortriptyline the weakest (White et al., 2007). Delirium has been reported to develop after abrupt discontinuation of fluoxetine (Blum et al., 2008) and with concomitant use of fluoxetine and lamotrigine (Chistyakova & Amos, 2008). In addition, concomitant use of low-dose bupropion sustained release and fluoxetine has been reported to be associated with delirium (Chan et al., 2006).

3.2.2.4. Other drugs

Benzodiazepines (Sanders, 2011), antipsychotics with strong anticholinergic effects (e.g. clozapine) (Centorrino et al., 2003), antiparkinson medications (i.e. levodopa) (Delmas et al., 2008) are among the other drugs that were reported to be associated with delirium. A systematic review of prospective studies that investigated the association between medications and risk of delirium reported that delirium risk appears to be increased with opioids, benzodiazepines, dihydropyridines and possibly antihistamine. The authors concluded that there appears to be no increased risk with neuroleptics or digoxin and there is uncertainty regarding H₂ antagonists, tricyclic antidepressants, antiparkinson medications, steroids, non-steroidal anti-inflammatory drugs and antimuscarinics (Clegg, A. & Young, 2011).

3.3. Pathophysiology

The pathophysiology of delirium is still poorly understood. The risk factors described above may act by similar mechanisms, leading to a common pathway that interferes with neurotransmitter function or with the supply or use of substrates to the brain (Maldonado, 2008). Imbalance in neurotransmitter systems is the leading hypothesized mechanism for delirium (Inouye, 2006). Other hypothesized mechanisms are neural injury, inflammation, and stress response (Hsieh et al., 2008).

3.3.1 Imbalance in neurotransmitter systems

3.3.1.1 Cholinergic deficiency

Cholinergic neurons play an important role in cognition and memory (Kopelman, 1986). Evidence from electroencephalographic and pharmacologic studies supports the role of cholinergic deficiency in genesis of delirium. Electroencephalographic studies have shown that delirium is associated with occipital slowing, peak power and alpha decrease, delta and theta power increase and slow wave ratio increase during active delirious states (Thomas et al., 2008). Cholinergic thalamo-cortical pathways responsible for attention, alertness and vigilance regulation modulate the basic EEG alpha rhythm (Nunez et al., 2001). Centrally acting anticholinergics result in a pattern very similar to the electroencephalographic findings in delirium (Renner et al., 2005; Sloan et al., 1992).

Pharmacologic studies have shown an association between delirium and administration of anticholinergic drugs and serum anticholinergic activity (Inouye, 2006). High serum anticholinergic activity is associated with severity of delirium (Mussi et al., 1999; Trzepacz, 1999). Also, the importance of cholinergic deficiency in pathophysiology of delirium is supported by studies showing that acetylcholine neurotransmission decreases with age, which is consistent with the finding that increasing age is a risk factor for delirium (Flacker & Lipsitz, 1999). Several mechanisms can result in cholinergic deficiency and predispose to delirium, including impairment in acetylcholine synthesis and cholinergic synaptic mechanisms, ischemia and global stressors and neurotransmitter imbalance (Hshieh et al., 2008).

3.3.1.2 Monoamine neurotransmitter system

Another neurotransmitter system supposed to have a role in pathogenesis of delirium is monoamine neurotransmitter system (Gaudreau & Gagnon, 2005). Dopamine, norepinephrine and serotonin have roles in arousal and sleep-wake cycle, they modulate physiological responses to stimuli (Robbins & Arnsten, 2009). This system, which is composed of three monoamine neurotransmitters, dopamine, norepinephrine and serotonin, has a balancing role for the cholinergic activity. The development of delirium involves interaction between these two neurotransmitter systems (Cole, 2004; Trzepacz & van der Mast, 2002). But instead of deficiency, dopamine excess has been reported to play a role in delirium (Moyer, 2011). It is suggested that dopamine increase during the stress of surgery can cause postoperative agitation and delusions in the patient. In laboratory studies, stress has been shown to elevate levels of mesocortical dopamine (Cassem et al., 2004). Haloperidol, a dopamine blocking agent has been used successfully to treat delirium for years (Moore & O'Keeffe, 1999).

Depending on the serotonin receptor bound, both serotonin excess and deficiency may be associated with cholinergic deficiency and predispose to delirium (Hshieh et al., 2008). Selective serotonin reuptake inhibitors like fluoxetine and bupropion have been reported to cause delirium (Chan et al., 2006). Delirium has been reported in a patient taking paroxetine preoperatively, the authors have contributed that postoperative delirium was indicating an adverse drug interaction involving, paroxetine (Stanford & Stanford, 1999).

3.3.2 Neural injury, inflammation, and stress response

Delirium has been hypothesized to result from increased release of proinflammatory cytokines in cases of trauma, infection or surgery (Eikelenboom et al., 2002; Rudolph et al.,

2008). Proinflammatory cytokines can affect the synthesis or release of acetylcholine, dopamine, noradrenaline and serotonin, and thereby increase the risk of delirium (Dunn, 2006). Also, these cytokines can stimulate responses from microglia, by this way cause inflammation in the brain (Dilger & Johnson, 2008). The effect of these proinflammatory cytokines do not appear to affect younger individuals with healthy brains, while the aging brain is more susceptible to the memory impairments produced by immune system activation (Staus, 2011).

4. Conclusion

Delirium is a common condition, especially in the elderly and in patients with severe illness. Delirium is associated with longer hospital stay, poorer functional outcome, and cognitive decline. Also, it is associated with elevated morbidity and mortality. Understanding etiology of delirium is important because treatment of delirium is identification and reversal of etiological factors. Etiological factors are of two types: predisposing and precipitating factors. The risk of delirium should be kept in mind when approaching to a patient with predisposing factors like increased age, cognitive impairment, hip fracture on admission and severe illness are among the most common ones. The presence of precipitating factors (the acute insults that trigger the mechanisms resulting in delirium) like anemia, hypoxaemia, electrolyte abnormalities, sleep deprivation, pain, bladder catheter use and drugs should be evaluated and be treated promptly if possible.

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