ASSOCIATION OF BRAIN-DERIVED NEUROTROPHIC FACTORS AND TAU PROTEIN BLOOD LEVELS WITH DELIRIUM PATIENTS IN INTENSIVE CARE UNIT

HOSPITAL UNIVERSITI SAINS MALAYSIA

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Introduction: Delirium is an acute and fluctuating disturbance of consciousness and cognition, that occurs in the majority of critically ill patients. It is hence associated with several diseases of severity and infection. As critically ill patients are subjected to numerous risk factors for delirium such as sedative, analgesic agents and pre-existing systemic illness, some of these may be modified to reduce the risk factors for delirium.

Objectives: The aim of the study was to determine the association between serum concentration of brain derived neurotrophic factor (BDNF) and Tau protein levels with delirium in mechanically ventilated ICU patients. Specific objectives included were 1) to compare the mean of length of stay (days) in ICU between the

delirious and non-delirious mechanically ventilated patients in ICU, 2) to compare the duration of mechanical ventilator usage (in days) between the delirious and non-delirious patients in ICU, and 3) to determine whether different age group is a factor that influences the level of BDNF and Tau Proteins among delirium patients.

Patients and Methods: This study was conducted in three phases: 1) the blood sampling within 12 hours and 48 hours of ICU admission, with subsequent centrifugation and storage of frozen plasma for the final testing using ELISA assay later, 2) the clinical diagnosis of delirium using the Confusion-Assessment Method in ICU (CAM-ICU), 3) a cross-sectional prospective study of 45 ICU patients to determine the associations between the blood levels of biomarkers which are Brain-derived Neurotrophic Factors and Tau protein with delirious patients who are mechanically ventilated in ICU (HUSM)

Results: The median BDNF levels were significantly lower in the delirium patients when compared to the non-delirium patients within the first day of admission, (71.22ng/mL, IqR 33.78 vs 103.76ng/mL IqR 41.91), p-value of 0.001. There was no significant difference in the median BDNF levels after 48 hours (day 3) from ICU admission between the delirious and non-delirious group, (8.69ng/mL, IqR 10.70 vs 12.16, IqR 10.79), respectively, with a *p*-value of 0.573. The median levels of Tau protein on day 1 and day 3, were not statistically significant for either the delirious and the non-delirious group, with day 1 ICU admission having Tau protein levels of 0.18ng/mL, IqR 0.12 vs 0.16ng/mL, IqR 0.10, and with day 3 ICU admission having delirum Tau protein levels of 84.66ng/mL, IqR 122.23 vs non-delirium Tau protein levels 55.48 ng/mL, IqR 30.9. The results show that there were significant differences

in the median length of stay between delirium and non-delirium groups, 11(7) and 5(6) respectively, with *p*-value of 0.003. The length of delirium patients requiring mechanical ventilator (in days) were significantly longer compared to the non-delirium patients, 9(7) and 3(5) respectively. In total, it was found that there were more ventilated patients in ICU having delirium at 57.5% (n=23) compared to 42.5% (n=17) for non-delirium patients. Median age of patients in ICU was 45 years old accounting 7.5% of all patients. Subsequent division of age range into three groups were done, with younger age from 18 to 35 years old, median age from 36 to 55 years old and older age from 56 to 65 years old. Out of 40 patients, 30%(n=12) were at the younger age group, 32.5% (n=13) were at median age group and 37.5% (n=15) were at the older age group. Among them, it was found that 57.5% (n=23) were delirious and 42.5% (n=17) were non-delirious. 34.78% (n=8) from the delirious group were at younger age, 26.1% (n=6) were at median age and 39.1% (n=9) were at older age. Further results show that among the 17 non-delirious patients, 23.5% (n=4) were at younger age, 41.8% (n=7) were at median age and 35.3% (n=6) were at older age.

Conclusion: This study demonstrates that there was an association between ICU admission levels of BDNF and the occurrence of delirium in ICU patients, in the pathophysiology of ICU delirium, suggesting a role for neuronal death occurring in the pre-ICU delirium setting or soon after admission of within 12 hours, and not during the ICU stay. However, Tau protein levels do not correlate with the occurrence of delirium in ICU HUSM.

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ABBREVIATIONS

ABG	Arterial blood gases
APACHE II	Acute Physiology and Chronic Health Evaluation II
BDNF	Brain-derived neurotrophic factors
CAM-ICU	Confusion Assessment Method in Intensive Care Unit
CNS	Central nervous system
C-tau	Cleaved tau
CRL	Central Research Laboratory
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-Linked Immunosorbent assay
HUSM	Hospital Universiti Sains Malaysia
IBM SPSS®	Statistical Package for the Social Sciences
ICU	Intensive Care Unit
MAPT	Microtubule-associate Protein Tau
O.D	Optical density
PKN	Protein Kinase N1
RASS	Richmond-Agitation Sedation Score
p value	Significant value
%	percent
^{o}C	degrees Celcius
μL	microliter
min	minutes
s	seconds
g	gravity
nm	nanometer
ng/mL	nanogram per mililiter
pg/mL	picogram per mililiter
rpm	rotation per minute

ABSTRAK

Tajuk: Hubungkait Antara Paras Protin *Brain-Derived Neurotrophic Factor* Dan Protin Tau Bagi Pesakit-pesakit Unit Rawatan Rapi Yang Mengalami Kecelaruan

Latarbelakang dan objektif:

Kecelaruan, iaitu suatu gangguan kesedaran dan kognitif yang akut dan turun naik, sering berlaku kepada pesakit-pesakit yang kritikal dan berlaku sehingga 80% daripada pesakit yang kritikal. Dengan itu, ia dikaitkan dengan beberapa tahap penyakit dan jangkitan. Oleh kerana pesakit-pesakit kritikal adalah terdedah kepada banyak faktor-faktor risiko untuk kecelaruan seperti ubat penenang, agen analgesik dan penyakit-penyakit sistemik yang sedia ada, sesetengah daripadanya boleh diubahsuai untuk mengurangkan risiko kecelaruan. Kajian ini adalah untuk menghubungkaitkan paras darah untuk *Brain-derived neurotrophic factors* dan Protin Tau dengan pesakit-pesakit yang mengalami kecelaruan semasa diberi bantuan pernafasan mekanikal di Unit Rawatan Rapi HUSM.

Metodologi:

Ini adalah kajian prospektif keratan rentas (*cross* section)yang telah dijalankan di Unit Rawatan Rapi HUSM daripada bulan Jun 2013 sehingga November 2013. Sebanyak 45 orang pesakit unit rawatan rapi tidak kira samada mengalami kecelaruan atau tidak telah terlibat didalam kajian ini. Di dalam tempoh 12 jam daripada waktu kemasukan unit rawatan rapi, darah telah diambil untuk analisa penanda bio-asas dan 48 jam seterusnya, satu lagi sampel darah telah diambil. Kecelaruan telah didiagnosa dengan menggunakan kaedah *Confusion-Assessment Method in ICU* (CAM-ICU). Asai ELISA

untuk plasma Protin Tau dan BDNF telah dilakukan untuk mendapatkan paras darah untuk penanda bio. Untuk mendapatkan hubungkaitan di antara paras darah penanda-bio iaitu Brain-derived neurotrophic factors dan Protin Tau dengan pesakit yang mengalami kecelaruan, analisa *non-parametric* telah dilaksanakan.

Keputusan:

Seramai 45 pesakit-pesakit telah dipilih untuk kajian ini, tetapi 5 daripada mereka telah digugurkan kerana CAM-ICU tidak dapat dilaksanakan ke atas mereka disebabkan pelalian yang mendalam dengan skor RASS di antara -4 ke -5. Sehingga ke akhir tempoh berada di Unit Rawatan Rapi, semua subjek yang digugurkan telah meninggal dunia. Pesakit-pesakit diantara umur 18 hingga 65 tahun secara dermografik telah dipilih untuk menyertai kajian ini. Didapati median untuk paras darah BDNF bagi mereka yang mengalami kecelaruan adalah rendah secara signifikannya, berbanding dengan pesakit yang tidak mengalami kecelaruan pada hari pertama kemasukan ke Unit Rawatan Rapi, (71.22ng/mL, IqR 33.78 vs. 103.76ng/mL, IqR 41.91) dengan nilai-p bersamaan 0.001. Didapati, tiada perbezaan secara signifikan di antara pesakit yang mengalami kecelaruan dengan yang tidak mengalami kecelaruan bagi median paras darah BDNF) setelah kemasukan ke Unit Rawatan Rapi 48 jam kemudian, iaitu masing-masing dengan median BDNF (8.69ng/mL, IqR 10.70 vs.12.16, IqR 10.79),nilai-p=0.573. Manakala, bagi median paras darah Protin Tau pada hari pertama kemasukan dan seterusnya hari kedua selepas kemasukan ke Unit Rawatan Rapi, tiada langsung hubungkaitan di antara paras darah Protin Tau untuk pesakit yang mengalami kecelaruan dengan yang tidak mengalami kecelaruan, dengan paras darah Protin Tau pada hari pertama kemasukan ke Unit Rawatan Rapi adalah 0.18ng/mL, IqR 0.12 vs. 0.16ng/mL, IqR 0.10, dan paras darah Protin Tau pada hari kedua selepas kemasukan

ke Unit Rawatan Rapi untuk pesakit yang mengalami kecelaruan adalah 84.66ng/mL, IqR 122.23 vs. 55.48ng/mL, IqR 30.95 untuk pesakit yang tidak mengalami kecelaruan, dengan nilai-p>0.005.

Umur median bagi pesakit-pesakit di Unit Rawatan Rapi adalah 45 tahun iaitu 7.5% daripada jumlah keseluruhan pesakit. Seterusnya, pembahagian lingkungan umur kepada 3 kumpulan telah dilakukan, dengan kumpulan usia muda di antara 18 hingga 35 tahun, kumpulan usia pertengahan di antara 36 hingga 55 tahun dan kumpulan usia lanjut di antara 56 ke 65 tahun. Daripada 40 pesakit, 30%(n=12) adalah kumpulan muda, 32.5% (n=13) adalah daripada usia pertengahan dan 37.5% (n=15) adalah daripada kumpulan usia lanjut. Daripada jumlah keseluruhan kumpulan tersebut, didapati 57.5% (n=23) telah mengalami kecelaruan dan 42.5% (n=17) adalah yang tidak mengalami kecelaruan. 34.78% (n=8) daripada kumpulan yang mengalami kecelaruan pula terdiri daripada kumpulan usia muda, 26.1% (n=6) adalah daripada kumpulan usia pertengahan dan 39.1% (n=9) terdiri daripada kumpulan berusia lanjut. Keputusan yang diperolehi juga menunjukkan perbezaan yang ketara (signifikan) pada median jangkamasa berada di Unit Rawatan Rapi di antara kumpulan yang mengalami kecelaruan dengan yang tidak mengalami kecelaruan, iaitu masing-masing 11(7)hari dan 5(6) hari, dengan nilai p=0.003. Jangkamasa pesakit yang mengalami kecelaruan bergantung kepada mesin bantuan pernafasan (jumlah hari) adalah lebih lama berbanding dengan mereka yang tidak mengalami kecelaruan, iaitu masing-masing 9 (7) hari dan 3(5) hari, dengan nilai-p=0.002. Secara keseluruhannya, didapati lebih ramai pesakit yang diberi bantuan pernafasan mekanikal di Unit Rawatan Rapi untuk mengalami kecelaruan iaitu 57.5% (n=23) berbanding dengan 42.5% (n=17) pesakit yang tidak mengalami kecelaruan, dengan nilai-p=0.002.

Konklusi:

Kajian ini menunjukkan bahawa terdapatnya hubungkaitan di antara paras darah BDNF dengan kejadian pesakit mengalami kecelaruan semasa kemasukan ke Unit Rawatan Rapi. Ini menunjukkan bahawa kecelaruan yang dialami mungkin telah berlaku sebelum kemasukan pesakit ke Unit Rawatan Rapi, dan mencadangkan peranan kematian neuron-neuron yang mungkin telah berlaku sebelum kemasukan atau sejurus selepas kemasukan ke Unit Rawatan Rapi dalam tempoh 12 jam terawal, dan bukannya sepanjang tempoh pesakit berada di Unit Rawatan Rapi. Walaubagaimanapun, paras darah Protin Tau didapati tiada berhubungkait dengan kejadian pesakit mengalami kecelaruan di Unit Rawatan Rapi.

ABSTRACT

Title: Association of Brain-Derived Neurotropic Factors and Tau Protein Blood Levels with Delirium Patients in Intensive Care Unit

Background:

Delirium, an acute and fluctuating disturbance of consciousness and cognition, frequently occurs in critically ill patients, occurring up to 80% of the critically ill. It is hence associated with several disease severity and infection. As critically ill patients are subjected to numerous risk factors for delirium such as sedative, analgesic agents and pre-existing systemic illness, some of these may be modified to reduce the risk factors for delirium. The aim of the study was to determine the association between serum concentration of brain derived neurotrophic factor (BDNF) and Tau protein levels with delirium in mechanically ventilated ICU patients.

Methodology:

This was a prospective cross-sectional study from June 2013 until November 2013 done in ICU HUSM. 45 ICU patients with or without delirium were included. Within 12 hours of ICU admission, blood was obtained for baseline biomarker analysis and subsequently 48 hours later, another blood sample was obtained. Delirium was diagnosed by using the Confusion-Assessment Method in ICU (CAM-ICU). ELISA assay for the plasma Tau protein and BDNF were performed to obtain the blood level for these biomarkers. To determine the associations between the blood levels of biomarkers which are Brain-derived Neurotrophic Factors and Tau protein with

delirious patients who are mechanically ventilated in ICU (HUSM), non-parametric analysis were performed.

Results:

45 patients were included into this study but 5 were dropped out due to inability to perform CAM-ICU as a result of deep sedation with RASS score ranging from -4 to -5. Until the end of their stay, all drop outs died in ICU. Demographically, patients from the age 18 to 65 years old were included. We found that the median BDNF levels were significantly lower in the delirium patients when compared to the non-delirium patients within the first day of admission, (71.22ng/mL, IqR 33.78 vs 103.76ng/mL IqR 41.91) with p-value of 0.001. There was no significant difference in the median BDNF levels after 48 hours (day 3) from ICU admission between the delirious and non-delirious group, (8.69ng/mL, IqR 10.70 vs 12.16, IqR 10.79), respectively, with a *p*-value of 0.573.However, for the median of Tau protein on day 1 and day 3, the levels were not statistically significant for either the delirious and the non-delirious group, with day 1 ICU admission having Tau protein levels of 0.18ng/mL, IqR 0.12 vs 0.16ng/mL, IqR 0.10, and with day 3 ICU admission having delirum Tau protein levels of 84.66ng/mL, IqR 122.23 vs non-delirium Tau protein levels 55.48 ng/mL, IqR 30.95, with *p*-value > 0.005.

Median age of patients in ICU was 45 years old accounting 7.5% of all patients. Subsequent division of age range into three groups were done, with younger age from 18 to 35 years old, median age from 36 to 55 years old and older age from 56 to 65 years old. Out of 40 patients, 30%(n=12) were at the younger age group, 32.5% (n=13) were at median age group and 37.5% (n=15) were at the older age group. Among them,

it was found that 57.5% (n=23) were delirious and 42.5% (n=17) were non-delirious. 34.78% (n=8) from the delirious group were at younger age, 26.1% (n=6) were at median age and 39.1% (n=9) were at older age. Further results show that among 17 non-delirious patients, 23.5% (n=4) were at younger age, 41.8% (n=7) were at median age and 35.3% (n=6) were at older age. The results show that there were significant differences in the median length of stay between delirium and non-delirium groups, 11(7) and 5(6) respectively, with *p*-value of 0.003.The length of delirium patients requiring mechanical ventilator (in days) were significantly longer compared to the non-delirium patients, 9(7) and 3(5) respectively, with a p-value of 0.002.

In total, it was found that there were more ventilated patients in ICU having delirium at 57.5% (n=23) compared to 42.5% (n=17) for non-delirium patients.

Conclusion:

This study demonstrates that there was an association between ICU admission levels of BDNF and the occurrence of delirium in ICU patients, in the pathophysiology of ICU delirium, suggesting a role for neuronal death occurring in the pre-ICU delirium setting or soon after admission of within 12 hours, and not during the ICU stay. However, Tau protein levels do not correlate with the occurrence of delirium in ICU.

CHAPTER ONE

INTRODUCTION

1.1. Background

Delirium is defined as an acute change or fluctuation in mental status, inattention, and disorganised thinking or an altered level of consciousness. Delirium is a common manifestation of acute brain dysfunction in mechanically ventilated patients in ICU and can occur up to 60-80% of mechanically ventilated ICU patients (Gunther et al 2008). Various factors were identified for delirium such as metabolic disturbances, extreme old age, baseline cognitive impairment, sepsis, hypoxaemia, sleep disturbances, medications such as anticholinergics, sedatives and analgesic medications of opioid based.

The diagnosis of delirium can be primarily tested clinically and is based on meticulous bedside observation of key features with two-step process. First of all, the level of arousal is measured and if patient is arousable, CAM-ICU is used for delirium detection. CAM-ICU is an abbreviation for the Confusion Assessment Method for the Intensive Care Unit, which was designed and validated in concert with long-standing delirium experts in Geriatrics and Neuropsychology such as Dr. Sharon Inouye, Dr. Joseph Francis, and Dr. Robert Hart in 2001. (www.icudelirium.org/docs). CAM-ICU is an excellent diagnostic tool in critically ill ICU patients to assess delirium. It is a clinical evaluation for delirium, which involves linking sedation and delirium monitoring using a two-step approach to assess consciousness (Refer **Figure 2.1** Linking RASS and CAM-ICU in a two-step assessment).

Apart from clinical evaluation for delirium, biomarkers such as Tau Protein and Brain-derived Neurotrophic Factor (BDNF) levels can be correlated with clinical findings in ICU. Neurotrophin is a neurotrophic factor whereas neurotrophic factor is a form of neuropeptides that act as nerve growth factor that regulates the growth, differentiation, and survival of certain neurons in the peripheral and central nervous systems (www.merriam-webster.com). Therefore, BDNF is a form of neuropeptides derived from the brain that act as nerve growth factor that regulates the growth, differentiation and survival of certain neurons. Tau Protein on the other hand is a protein that binds to and regulates the assembly and stability of neuronal microtubules and that is found in an abnormal form as the major component of neurofibrillary tangles (www.merriam-webster.com). Tau Proteins are implemented in clinical trials to reflect biological activity, mechanisms of action of compounds, support enrichment of target populations, provide endpoints for proof-of-concept and confirmatory trials on disease modification. (Hampel *et al* 2010). Tau represents the subunit protein of one of the major hallmarks of Alzheimer disease (AD), the neurofibrillary tangles, and is therefore of major interest as an indicator of disease mechanism. (EM Mandelkow *et al* 2012).

BDNF has long been known to be critical for the growth and survival of neurons and Tau Protein. It has a direct corelationship with the severity of dementia, which suggests that BDNF and pathological Tau Proteins are reliable marker of the neurodegenerative process, possibly including delirium. (Buée *et al* 2000; Gunther *et al* 2008). The recent discovery of tau gene mutations in fronto-temporal dementia with parkinsonism linked to chromosome 17 (FTDP-

17) has reinforced the predominant role attributed to Tau Proteins in the pathogenesis of neurodegenerative disorders, and underlined the fact that distinct sets of tau isoforms expressed in different neuronal populations could lead to different pathologies. (Buée et al 2000).

However, for identification of delirium, risk factors of delirium need to be identified and routine laboratory tests such as full blood count (FBC), arterial blood gas (ABG), serum electrolytes, blood urea nitrogen (BUN), urine drug screens, liver function tests (LFT), glucose level, ECG, CXR and blood cultures are also important.

Since delirium has been poorly diagnosed due to the misleading understanding of delirium, the condition is often unrecognised due to many clinicians attributing delirium symptoms to dementia or depression.

Given that delirium is the most commonly occurring in the critically ill patients in ICU up to 20-80%, depending on the severity of the illnesses, hence, it is important to diagnose and manage this dysfunction by implementation of validated screening tools and pharmacological treatment.

We hope by conducting this study, detection of delirium can be improved and help to reduce morbidity and mortality as delirium is associated with poor short-term outcomes and may result in adverse sequelae years after ICU discharge.

1.2. Rationale of the study

Given that the incidence of delirium in the critically ill patients is the most common incidence occurring in ICU of up to 20-80%, depending on the severity of the illnesses and its association with consequential worse acute and chronic sequelae, it is therefore important to diagnose and manage this dysfunction by implementation of validated screening tools and pharmacological treatment (Gunther et al 2008).

The reason that Tau protein and Brain-Derived Neurotrophic Factors were selected for the determination of delirium from plasma is that both biomarkers can be correlated with clinical findings in ICU.

The most commonly used sandwich ELISA kit shows a good specificity (90%) and sensitivity (81%), discriminating Alzheimer's disease and controls (S Schaer-Marschke *et al* 2008). Therefore, this study is reproducible at any time for the detection of delirium, as delirium is a part of acute brain dysfunction that somehow mimic neurodegenerative diseases such as Alzheimer's disease.

1.3. Objectives of the study

1.3.1. General objective:

To determine the correlation of the blood level of Tau protein and BDNF with patients having delirium in ICU.

1.3.2. Specific objectives:

a. To compare the mean blood levels of Tau protein and BDNF between the delirious and non-delirious mechanically ventilated patients in ICU.
b. To compare the mean of length of stay(days) in ICU between the delirious and non-delirious mechanically ventilated patients in ICU.
c. To compare the duration of mechanical ventilator usage (in days) between the delirious and non-delirious patients in ICU.
d. To determine whether different age group is a factor that influences the level of BDNF and Tau Proteins among delirium patients.

CHAPTER TWO

LITERATURE REVIEW

2.1. Delirium

2.1.1. Definition

Delirium is an acute change in mental status marked by a fluctuating course of impaired attention, disorganised thinking, and disturbance of consciousness. In the American Psychiatric Association's (APA) Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), delirium is defined as a disturbance of consciousness and cognition that develops over a short period of time (hours to days) and fluctuates over time.

Historically, a myriad of terms such as acute confusional state, ICU psychosis, ICU syndrome, acute brain dysfunction and encephalopathy have been used to describe delirium. The word 'delirium' was first used as a medical term as early as the first century AD to describe mental disorders occurring during fever or head trauma (Chadwick J.1950). Delirium is used as a standard term for a diverse range of conditions, including acute confusional state, acute brain syndrome, acute cerebral insufficiency and toxic–metabolic encephalopathy. Over time, the term delirium has evolved to describe a transient, reversible syndrome that is acute and fluctuating, and which occurs in the setting of a medical condition (Fong et al 2009).

However, nowadays the critical care literature has started to conform to the recommendations of experts and the APA that the term delirium to be used uniformly to describe this brain dysfunction syndrome. A lot of times delirium is under diagnosed and have been poorly documented in the intensive care settings due to the perception that patients who are critically ill in ICU are well sedated and comfortable. Furthermore, delirium is often unrecognised by clinicians or incorrectly attributed to depression, dementia or considered as an expected, inconsequential complication of critical illness. Given that delirium is the most common organ dysfunction to be found in critically ill patients in ICU and is associated with consequential worse acute and chronic sequelae, hence, it is important to diagnose and manage this disease by implementation of validated screening tools.

2.1.2. Prevalence and subtypes

The prevalence rates of delirium can be as high as 60-80% based on the reports in medical and surgical ICU cohort studies. (Gunther *et al* 2008). This observation was made depending upon the severity of illness and the diagnostic methods used. There are two different pathways that exist in inflamed and non-inflamed Intensive Care Unit patients who are found to be delirious. Lipowskiin 1983 described a more useful clinical category that can be categorised into subtypes according to psychomotor behaviour as follows:

a. Hypoactive delirium
b. Hyperactive delirium
c. Mixed delirium

The characteristics for hypoactive delirium includes decreased physical and mental inattention, decreased responsiveness, appear more withdrawn and apathic. Patients in ICU may be sluggish and lethargic, stuporous and may be associated with a worse prognosis. This high prevalence of hypoactive delirium in critically ill patients probably contributes to clinician's lack of recognition of delirium.

For hyperactive delirium, it is characterised by agitation, restlessness, combativeness and emotional liability. Manifestations of hyperactive delirium include groping or picking at the bedclothes or attempting to get out of bed at an inappropriate time which could cause harm and untimely damage to patients (Girard *et al* 2008). This exposes both patients and caregivers at risk for serious injuries. However, this form of delirium occurs only in the minority of critically ill patients. A cohort study done by Peterson and coworkers observed that purely hyperactive delirium was rare of 1.6%, whereas 43.5% of patients in ICU had hypoactive delirium and 54.1% had mixed delirium. Among non-ICU patients, hyperactive delirium has been associated with a better prognosis than hypoactive delirium, but it has not been evaluated thoroughly among ICU patients (Girard *et al* 2008).

2.1.3. Diagnosis of delirium in ICU

Despite that patients when admitted to the ICU are mechanically ventilated, sedated and critically ill, delirium can be assessed by linking sedation and delirium monitoring using a two-step approach to assess consciousness, as shown in the diagram below.

Figure 2.1 Linking RASS and CAM-ICU in a two-step assessment

Step One: Sedation assessment

The Richmond Agitation and Sedation Scale: The RASS*

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movement not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert but has sustained awakening (eye opening/eye contact) to voice (≥ 10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation	Physical Stimulation
-5	Unarousable	No response to voice or physical stimulation	

Procedure for RASS Assessment

1. Observe patient.
   a. Patient is alert, restless or agitated (score 0 to +4)

2. If not alert, state patient's name and say to open eyes and look at speaker.
   a. Patient awakens with sustained eye opening and eye contact. (score -1)
   b. Patient awakens with eye opening and eye contact but not sustained (score -2)
   c. Patient has any movement in response to voice but no eye contact (score -3)

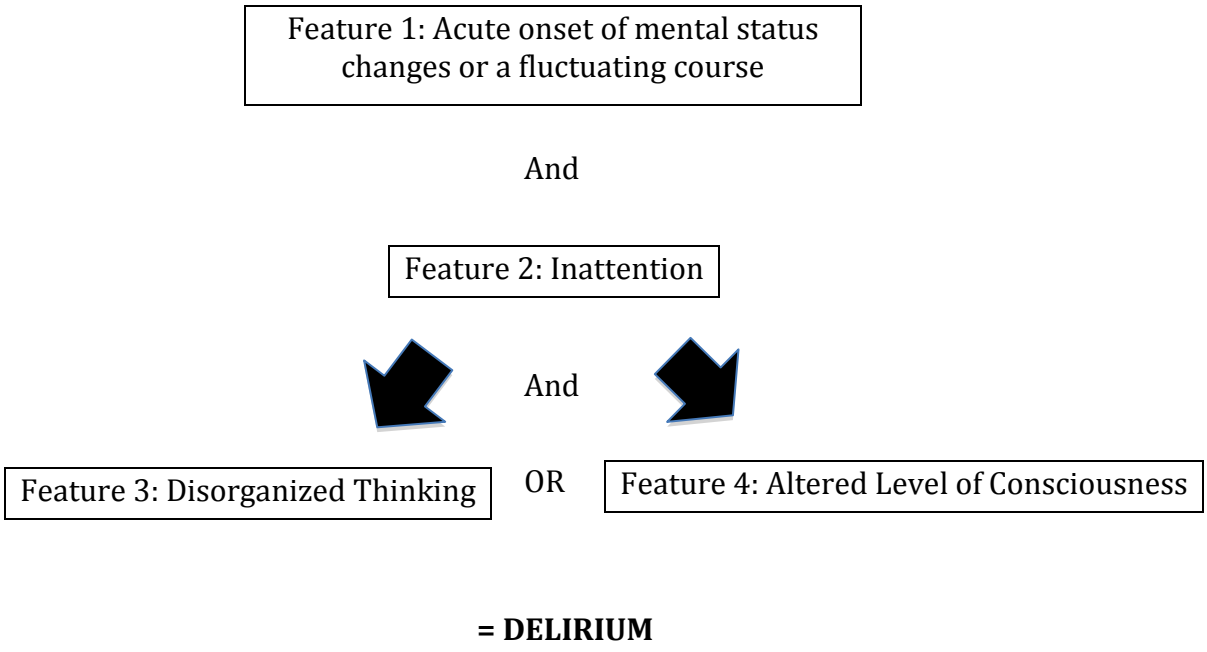
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.

   a. Patient has any movement to physical stimulation (score -4)
   b. Patient has no response to any stimulation (score -5)

If RASS is -4 or -5, then Stop and Reassess patient at a later time.
If RASS is above -4 (-3 through +4) the Proceed to Step 2.

*Sessler, et al. AJRCCM 2002; 166:1338-1334. Ely, et al. JAMA 2003; 289:2983-2991

Step Two: Delirium Assessment



= DELIRIUM