Pathogenesis of Delirium

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Considering physiopathological processes of delirium, it is possible to see that numerous precipitating and predisposing factors, each of which would facilitate development of delirium, are interacting with each other in the majority of cases. As conventional electrophysiological tests, brain imaging, and neurotransmitter analyses are not always possible in the cases and the results of animal studies do not overlap one to one, physiopathological mechanisms of delirium have not been enlightened yet (Isik 2014).

Diversity of defined risk factors and neurochemical abnormalities suggests that brain dysfunction in delirium results from the interaction among numerous systems. Therefore, it seems impossible to explain delirium by a single etiological theorem. However, evidences that delirium is a neurotoxic picture which develops due primarily to neurotransmitter (cholinergic insufficiency) and inflammatory (increase in stress response/neuroinflammation) mechanisms (Matto et al. 2010) are increasing each passing day (Mac Lullich et al. 2009).

Since the basic problem in the disease is the maintenance of attention, trying to understand the neurobiology of attention would be the best approach (Isik 2014). Normal attention function requires integrity of the ascending reticular activating system (ARAS) in the superior part of the brain stem and polymodal association areas in the cortex. Stimulation of ARAS enables alertness; whereas destruction may cause sleep, coma, and akinetic mutism. ARAS directs the cortex for stimulus uptake; polymodal association areas focus and control the alertness energy necessary for attention. Prefrontal cortex and posterior parietal cortex play an important role in the regulation of attention. Prefrontal cortex primarily enables the maintenance of attention. Risk factors defined for delirium may cause various confusional states by

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impairing the ascending effect of ARAS and descending control of frontal, parietal, and limbic cortex on attention and/or by influencing regulation of area-specific attention functions (Isik 2009, 2014). Studies on evoked potentials of brain stem and on brain imaging indicate that not only the cortical structures but also subcortical structures such as thalamus, basal ganglia, and pons reticular formation play an important role in the pathogenesis of delirium (Cerejeir et al. 2010). ARAS influences cerebral cortex both directly and by means of thalamic nuclear signals; therefore, delirium may observed even with small lesions in thalamus.

Similar condition can develop in case of dysfunction of basal ganglia, which are responsible for multidirectional connection between thalamus, brain stem, and cerebral cortex. Delirium being more prevalent in basal ganglion diseases such as subcortical stroke and Parkinson's disease supports this hypothesis (Trzepacz 1994; Benbadis et al. 1994).

Chaotic process in delirium is observed not only in the anatomy of the disease but also in the physiopathology just as the same. Therefore, we consider that discussing the mechanisms that focus on in the development of delirium under separate topics would be beneficial.

2.1 Dysfunctions Associated with Neurotransmitters

It is thought that documented etiological factors of delirium act over similar mechanisms by altering functions of neuronal membrane and leading to a series of neurotransmitter abnormalities. Probably, delirium results from the interaction between numerous neurotransmitters, mainly acetylcholine and dopamine, and cortical and subcortical pathways. Any situation that influences function, synthesis, and secretion of neurotransmitters can lead to delirium (Mittal et al. 2011).

According to the neurotransmitter hypothesis, etiological factors cause neurotransmitter abnormalities by impairing cerebral oxidative metabolism, and consequently cerebral dysfunction occurs. Decrease in cholinergic activity and increase or decrease in serotonergic and γ-aminobutyrinergic (GABAergic) activity due to oversecretion of dopamine, norepinephrine, and glutamate may be effective in delirium presenting itself with different symptoms (Matto et al. 2010; Van Der Mast 1998).

2.1.1 Acetylcholine

It is not surprising that cholinergic system, which is important for attention and cognitive functions, plays a role also in the development of delirium. Current evidences suggest that cholinergic system is effective in the development of delirium. While anticholinergics facilitate development of delirium, severity of delirium clinic is enhanced with the intensity of drug-related anticholinergic activity (Martins and Fernandes 2012). Since acetylcholine (ACh), which is the basic transmitter of cholinergic system, is synthesized from "acetyl coenzyme A" by an ATP-dependent reaction, acetylcholine production is in close association with energy cycle of the neurons. Therefore, cerebral ACh production is influenced by any condition that affects

oxidative metabolism such as hypoxia or inflammation. ACh insufficiency that results from neuronal loss in cholinergic system may be a reason for tendency to delirium in dementia cases (Terry and Buccafusco 2003). In brief, neurotransmitter imbalances due to the factors such as ischemia and global stressors and impairment in acetylcholine synthesis and cholinergic synaptic mechanisms lead to cholinergic insufficiency and consequently to delirium, no matter how diverse the etiological factors are (Mittal et al. 2011; Hshieh et al. 2008). Despite the presence of very strong evidences supporting cholinergic insufficiency hypothesis, this hypothesis has weaknesses. For example, benefits of cholinesterase inhibitors in the treatment of delirium are limited. Moreover, why clinical presentation of Alzheimer disease and delirium is different (attention disorder in delirium, memory disorder in Alzheimer disease) although they are physiopathologically associated with each other cannot be explained completely (Hshieh et al. 2008). On the other hand, that patients with postoperative delirium have lower plasma cholinesterase levels in the preoperative period has brought potential to the acetyl and butyrylcholinesterase enzymes for being biomarkers of postoperative delirium. This result may explain why cholinesterase inhibitors are not as much effective as expected in the treatment of delirium (Cerejeira and Mukaetova-Ladinska 2011).

2.1.2 Dopamine

Acetylcholine hypothesis should be considered together with dopamine hypothesis as they have close relationship in the brain. The conditions with increased dopamine levels cause development of delirium. Dopamine is effective in the occurrence of delirium clinic, primarily of the psychotic symptoms, by playing a role in motor activity and cognitive functions such as attention, thinking, and perception (Van Der Mast 1998). Dopamine blockers are used in the treatment of delirium until the underlying causes are improved as they help temporary balance of acetylcholinergic and dopaminergic activities. These drugs provide temporary improvement until underlying reasons are improved (Mittal et al. 2011). Studies demonstrated that dopamine antagonists caused motor hyperactivity similar to that in hyperactive delirium and EEG revealed low wave pattern. Increased dopamine usually causes appearance of the symptoms such as increase in psychomotor activity, irritability, agitation, disturbance, aggressiveness, and psychosis (Maldonado 2008).

Although the effects of the other neurotransmitters such as GABA, serotonin (5-hydroxytryptamine [5HT]), and norepinephrine have not been as well documented as that of acetylcholine and dopamine, their contribution to the development of delirium is known (Mittal et al. 2011).

2.1.3 Serotonin

Serotonin (5HT) is an important neurotransmitter in the development of delirium in both surgical and medical patients. Synthesis and secretion of 5HT in the brain depend on the presence of tryptophan, which is the precursor of 5HT (Maldonado 2008). Increase and decrease in serotonergic activity are effective in the

development of delirium. It is determined that serotonergic activity is particularly decreased in hyperactive delirium and increased in hypoactive delirium. Human and animal studies demonstrate that serotonin concentrations increased in hepatic encephalopathy and septic delirium (White 2002). Extremely increased serotonergic activity causes occurrence of psychotic symptoms, which are among the basic symptoms of serotonergic syndrome and delirium. On the other hand, decrease in cerebral tryptophan level and accordingly decrease in serotonergic functions have been determined in delirium tremens. Therefore, neuropsychiatric symptoms just like in delirium clinic are quite common in conditions which selective serotonin reuptake inhibitors are withdrawn too quickly (Maldonado 2008).

2.1.4 Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is the main inhibitor neurotransmitter of the central nervous system (CNS). Agents like propofol and benzodiazepines, which are frequently used in hospitals and intensive care units, show high affinity to GABAergic receptors, particularly in the brain stem. Cerebral functional integrity is impaired, and maintenance of alertness becomes difficult as the result of excessive neurotransmission in the CNS (Maldonado 2008). While GABA activity is increased in hepatic encephalopathy, it is decreased in delirium due to barbiturate withdrawing (Weinberger 1993). Increase in ammonium concentration in the patients with hepatic encephalopathy causes increase in glutamate and glutamine, which are the precursors of GABA. Hyperactivity of locus coeruleus and its noradrenergic neurons is in question in delirium due to alcohol withdrawing (White 2002).

2.1.5 Glutamate

Glutamate is the neurotransmitter of N-methyl-D-aspartate (NMDA) receptors in the CNS. Ischemic injury allows Ca^{+2} transport into the cell and accordingly causes significant increase in extracellular glutamate levels and glutamate receptor activation. Excitatory glutamate that is increased under hypoxic conditions activates NMDA receptors and may cause neuronal injury. Nevertheless, dopamine is required for glutamate toxicity, which is also known as Ca^{+2}-related neurotoxicity. When dopamine reaches to high levels, it may enhance excitatory effect of glutamate by causing adequate neuron depolarization for the activation of voltage-dependent NMDA receptors. Overstimulation of NMDA receptors as well causes neuronal injury and death (Maldonado 2008).

2.2 Inflammatory Response

Delirium can accompany many medical and surgical conditions with increased inflammatory response. Therefore, delirium may manifest itself sometimes as a condition that accompany sepsis-related multi-organ failure (Siami et al. 2008), sometimes as a presenting clinic of underlying simple urinary system infection or

pneumonia (particularly in elder dementia patients) and sometimes as a postoperative complication (O'Keeffe and Chonchubhair 1994).

2.2.1 Cytokines

Systemic inflammatory processes are associated not only with delirium but also with more remarkable neuropsychiatric symptoms. Neuropsychiatric symptoms similar to delirium have been defined long time ago in the patients treated with recombinant IFN (Malek-Ahmadi and Hilsabeck 2007; Cole et al. 2003). Bacterial endotoxin has dose-dependent effect on cognitive functions, emotional state, and sleep in healthy volunteers (Mullington et al. 2000; Reichenberg et al. 2001). Circulating cytokines increase even with very low doses of lipopolysaccharides (LPS) (0.2 ng/kg), and this unfavorably influences the declarative memory and psychomotor activities (Krabbe et al. 2005; Brydon et al. 2008).

It is considered that cognitive changes occur in acute systemic inflammation due to impaired cellular and molecular synergistic relationships in different regions of the brain especially in hippocampus (Tizard 2008). It is known that proinflammatory IL-1 has an important role in neurophysiological processes in memory consolidation probably in the way to regulate synaptic plasticity (Rachal Pugh et al. 2001). IL-6 is effective in hippocampal dysfunction, too (Sparkman et al. 2006). Contrarily, IL-10 balances effects of IL-1 and IL-6, and this seems like to prevent behavioral and cognitive harmful effects of cytokines (Krzyszton et al. 2008; Richwine et al. 2009). In delirium, decrease in the expression of hippocampal brain-derived growth factor (BDGF) and increase in mitochondrial dysfunction and oxidative stress are effective in neuroinflammation that cause learning and memory defects (Noble et al. 2007, Tanaka et al. 2006). All of this information suggests that local cerebral reactive oxygen species (ROS), proinflammatory cytokines, metalloproteinases, nitric oxide, and chemokines can impair learning and memory processes by influencing synaptic plasticity and long-term potentiation processes (McAfoose and Baune 2009).

It has been reported that microglia and astrocyte activation after peripheral immune response may lead to Bax/Bcl-2 imbalance and may influence survival of intraparenchymal brain cell (Semmler et al. 2005). Sharshar et al. (2003) reported that septic shock is associated with neuronal and glial apoptosis within the autonomic centers, which is strongly associated with endothelial inducible nitric oxide synthase (iNOS) expression. Lee et al. (2008) also demonstrated that neuroinflammation-associated amyloidogenesis activation might be an important mechanism associated with neurocognitive dysfunction triggered by apoptotic neuronal cell death and systemic immune stimuli. After peripheral immune stimulation, the cascade of events in the central nervous system can influence neuronal vitality even in the long-term period (Qin et al. 2007).

2.2.2 Cortisol

Cortisol is an essential hormone for stress response of the body. Stress response of cortisol increases and duration of response is prolonged in senility and

neurodegeneration in dementia (Martins and Fernandes 2012). In the studies, it was determined that cortisol increases not only in blood but also in CSF in delirium patients (Mittal et al. 2011). As excessive glucocorticoid secretion negatively influences mood and memory, they are considered to be effective on pathogenesis of delirium particularly in elderly patients. Excessive glucocorticoid also inhibits glucose transport into the neuron and accordingly neuronal energy deficiency emerges. This particularly affects hippocampus functions (Maldonado 2008). This information appears to explain both increased tendency to delirium and occurrence of delirium clinic in acute stress situations accompanied by high cortisol levels (Martins and Fernandes 2012). Moreover, those high plasma levels of many inflammatory markers, especially cortisol and IL-6, detected both before and during delirium support "extreme stress response/neuroinflammation hypothesis." The presence of relation between cholinergic system and innate immune system over cholinergic inflammatory pathway is an interesting point (Tracey 2009). The regulation of extreme stress response and neuroinflammatory pathway would open new horizons for the treatment of delirium in the future (Cerejeira et al. 2011).

2.3 Changes in Neuronal Injury and Permeability of Blood-Brain Barrier (BBB)

Trauma, surgical infection, and metabolic and ischemic reasons cause not only direct neuron injury in the brain but also delirium by increasing proinflammatory cytokines or impairing synthesis and secretion of neurotransmitters such as acetylcholine, dopamine, serotonin, and norepinephrine (Hshieh et al. 2008). In addition, systemic diseases that cause BBB injury may also accompany delirium. BBB injury or dysfunction causes the brain to be exposed to the effect of systemic inflammation (Dimitrijevic et al. 2006).

Factors that precipitate delirium both cause neuronal dysfunction or injury by directly influencing the brain and contribute to the development of an exaggerated inflammatory response. Risk factors of delirium intensively stimulate the limbic hypothalamo-pituitary-adrenal axis, cause immune system activation and stress response, and enhance permeability of BBB (Mittal et al. 2011).

Experimental studies demonstrated that peripheral inflammatory stimuli cause functional and molecular changes in BBB. Increase in permeability of BBB due to change in tight connection proteins has been reported in different inflammatory models. Likewise, peripheral LPS injection (the most commonly used model in inflammation) initiates the cascade of events that cause BBB injury in early period, overexpression of adhesion molecules in endothelial cells, and infiltration of blood leukocytes into the brain tissue (Cerejeir et al. 2010; Semmler et al. 2005; Hofer et al. 2008; Nishioku et al. 2009).

Postmortem studies of human brain tissue also determined mild correlation between systemic inflammation and activation of endothelial and perivascular cells (Uchikado et al. 2004). Although it is difficult to demonstrate BBB injury in human, β subunit of S100 protein (S100-β) can be considered as the evidence for increased

BBB permeability (Marchi et al. 2004). Many conditions, such as septic shock and cardiac surgery, are associated with acute systemic inflammation accompany with BBB (Ali et al. 2000; Gao et al. 1999; Nguyen et al. 2006). In such patients, it was demonstrated that increasing serum S100-β protein during delirium episodes could cause BBB injury (van Munster et al. 2010). In addition, detection of leukoencephalopathy on magnetic resonance imaging (MRI) of delirium cases which were in the early stage of septic shock supports BBB injury (Sharshar et al. 2007). In addition to systemic inflammation, other factors, such as microscopic structure and function, are influenced by hypoxia, ischemia, and pain (McCaffrey et al. 2009; Oztas et al. 2004).

IGF-I: Insulin-like growth factor I (IGF-I) is one of the proteins that play a role in the development of human body and in the regulation of various metabolic and brain functions. IGF-I levels decrease with age. IGF-I has an effective role in the development of BBB, neuronal excitability, synthesis of myelin sheath, blood vessel maturation, neuronal vitality, proliferation, differentiation, synaptogenesis, and transport and metabolism of cerebral glucose. IGF-I plays supporting role on neuronal plasticity. There are many studies reporting that IGF-I levels are low in delirium cases, and this low level is associated with the severity and duration of disease (Adamis et al. 2009). Mechanisms associated with the role of IGF-I, which has such metabolic effect, in the development of delirium are (Adamis and Meagher 2011):

Neuroprotective IGF-I: It may be effective in the pathogenesis of delirium due particularly to its cortical, hippocampal, and dopaminergic neuroprotective activity. IGF-I plays protective role for the neurons in the situations that lead to neurotoxicity such as hypoglycemia, hyperglycemia, β-amyloid toxicity, osmotic stress, deficiency of growth factors, low potassium and ceramide. Apoptosis is the mechanism which is most emphasized for cell death during neuronal injury. IGF-I prevents apoptosis by activating PI3K/Akt kinase and Ras/Raf/MEK/ERK pathways in the early phase and protein synthesis pathways (such as bcl-xL) in the late phase after neuronal injury. While decrease in IGF-I levels causes delirium by enhancing neuronal stress sensitivity, increased IGF-I levels may play an active role in the improvement of clinical.

Impairment in somatotropic axis: IGF-I plays an active role in GRH/somatostatin-growth hormone (GH)-IGF-I axis. GH has tropic effects on cognitive functions, mood, concentration, and general metabolism.

Glucocorticoids-cytokines: The facts that IGF-I is effective in the control of hypothalamo-pituitary-adrenal (HPA) axis and that increased glucocorticoids in delirium has decreasing effect on IGF-I expression are important for the development of delirium. Interaction between cytokines and IGF-I, oversensitivity of HPA axis in response to acute stress, and suppression of somatotropic axis may play a role in the development of delirium (Cerejeira et al. 2013).

2.4 Impairment in Sleep Pattern

Sleep is a process necessary for the regulation of physical and mental daily functions (Maldonado 2008). Biological clock and day light as well as melatonin are effective in the regulation of circadian rhythm of sleep. Melatonin is secreted from

pineal gland under the control of suprachiasmatic nucleus in response to darkness. In a study, it was demonstrated that low melatonin levels were associated with in advanced age, delirium, postoperative period, and in the intensive care unit patients in whom sleep-alertness cycle is impaired (de Jonghe et al. 2010). Impairment in sleep regulation may cause memory problems, and this may be effective in the development of delirium in all inpatients especially in intensive care units. In the event of chronic partial sleeplessness defined as sleeping less than 4 h each night for consecutive 5 days, it was also demonstrated impairment in attention, judgment, reaction time, and recall functions of memory. Moreover, emotional imbalance such as irritability and fluctuation of mood due to the impaired interaction between amygdala and prefrontal cortex has been reported in the event of sleeplessness for more than 36 h. Based on these findings, inadequate sleep may cause both psychosis and delirium. Inadequate sleep not only causes delirium but also enhances severity and prolongs the duration of already existing delirium. It was determined that disturbance of sleep-alertness cycle and nighttime alertness in delirium resulted from irregular melatonin secretion (Misra and Ganzini 2003).

Interaction between immune system and sleep is also very important. Cytokine synthesis of immune system plays an active role in normal sleep cycle. Decrease in natural killer cell count, antibody levels after influenza vaccination, IL-2 production, and lymphokine-activated killer cell activity were determined in the situations of both acute and chronic sleeplessness. In addition, inadequate sleep can also influence endocrine and metabolic functions by altering cortisol secretion pattern and glucocorticoid feedback regulation (Spiegel et al. 1999; Ozturk et al. 1999). All of these explain the close physiological relationship between sleep and delirium.

2.5 Genetic

Although genetic-delirium relationship has been investigated in a very few studies and despite the data that genetic profile may increase the risk of delirium, the relationship between delirium and apolipoprotein E4 allele has been evaluated in the majority of studies, but no relation could have been demonstrated. The genetics of delirium tremens has been investigated more frequently and emphasis has been put on three different genes which play a role in dopamine transmission. However, no significant relationship has been found yet between these genes and delirium in elderly patients (Van Munster et al. 2009).

2.6 Drugs

Drugs, which are one of the main topics of geriatrics practice, are one of the most common causes of delirium. Different groups of drugs can cause delirium; however, sedative-hypnotics with documented psychoactive effect, narcotics, and anticholinergic drugs are the most frequently encountered ones. Particularly using more than five drugs enhances the risk of delirium in elderly patients. Since the prevention of

development of disease is at least as important as treatment, drugs that facilitate development of delirium should be certainly known (Inouye 1998; Hubbard et al. 2013). It would be correct to say that the incidence of delirium in elderly patients will significantly decrease with discontinuation of psychoactive drugs in this population. The age-related changes in drug metabolism and elimination, as well as increase in the susceptibility against the drugs effective in the CNS, likely could be the cause of this (Lauretani et al. 2010). Other causes include:

- Polypharmacy
- Lack of information on drug-drug interaction in multiple drug usage
- Drug-disease interaction
- Age-related decrease in neurotransmitter production

Because many neurotransmitters, cytokines, and hormones take place in the pathogenesis of disease, it can be said that drugs that potentially influence these factors may play role in the development of delirium. In this topic, due to the plenty of the evidences that support cholinergic insufficiency, anticholinergic drugs should be taken account. In addition, the drugs that cause acetylcholine-dopamine imbalance in delirium should be kept in mind, too (Lauretani et al. 2010).

Digoxin unfavorably influences neuronal activity not only due to antimuscarinic effect but also by inhibiting membrane N-K-ATPase pump. Quinolone group antibiotics have mild dopaminergic effect as well as NMDA and GABA receptor antagonism. Morphine increases dopamine secretion and inhibits neuronal membrane N-K-ATPase pump. Histamine receptor blockers have both antimuscarinic effect and dopamine secretion. In addition, since alternative medicine is preferable for older people, hallucinogens such as mandrake, jimsonweed, and henbane among complementary medicines may also cause delirium (Alagiakrishnan and Wiens 2004).

It was reported that GABA transmission decreases and subsequently glutamate, NMDA, and dopaminergic and noradrenergic transmissions increase in delirium related to alcohol, sedative, or hypnotic withdrawn (Maldonado 2008).

In conclusion, all the etiological factors that play a role in the development of delirium unfavorably influence functional integration of cortical, prefrontal, and parietal networks, as well as subcortical structures such as basal ganglia, cerebellum, thalamic nuclei, and RAS. Furthermore, high cognitive processes such as attention, study memory, and administrative functions are impaired (Lauretani et al. 2010). However, pathogenesis of delirium has not been correctly explained by focusing only on a single mechanism (Watt et al. 2012; NICE 2010; Hovorka et al. 2012).

Personal tendency: Interaction between personal susceptibility and underlying reasons is important for risk factors of delirium considered as individual susceptibility. As defined in previous studies, while delirium can develop due to very simple reasons in high-risk cases as in older people, major causes may be enough to develop delirium in young, healthy, and low-risk cases (Inouye et al. 2014).

Iatrogenic factors: They are quite important in the development of delirium in elderly inpatients. Polypharmacy, anticholinergic drugs, and physical limitation at

the time of hospitalization, monitoring, and impaired sleep routine are effective in the development of delirium (Inouye et al. 2014).

Although, multiple physiopathological mechanisms that take place in delirium have not been completely exposed yet, risk factors and facilitators could have been detected clearly. This is particularly important for the determination of preventive approaches.

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