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Abstract

Delirium seems to result from the interaction between pre-operative patient vulnerabilities and exposure to precipitating factors. Post-operative delirium (POD) is often observed in elderly patients undergoing orthopedic surgery, particularly hip fracture repair and may persist for several days postoperatively. Emergence delirium (ED) is known as an acute agitation and confusion occurring during or immediately following emergence from general anesthesia, in the OR or post anesthesia care unit. Stress and inflammation are important triggers in the development of delirium.

Key Words: emergence delirium, delirium, cognitive impairment, acute confusional state, orthopaedic surgery.

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Introduction

The term delirium was used for the first time by Celsius to describe a cognitive deficit associated with fever or head trauma. Hippocrates in 500 BC introduced the term of phrenitis to describe the acute onset of mental abnormalities accompanied by a change in behavior, disturbances of sleep and cognitive deficit in patients experiencing fever [1].

At the end of the nineteenth century and the beginning of the twentieth century the general agreement was that the outcome of delirium was either death or full recovery [2].

During the twentieth century EEG recording performed in patients diagnosed with delirium found a reduction of cerebral metabolic rate, indicated by an increase in slow wave activity [3].

Delirium is defined by the DSM-V as a disturbance in attention

and awareness according to several criteria [4]:

- A. "Disturbance in level of awareness and reduced ability to direct, focus, sustain, and shift attention (this represents a minor change from: Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention).
- B. A change in cognition (such as deficits in orientation, executive ability, language, visuoperception, learning and memory).
 - Cannot be assessed in face of severely reduced level of awareness
 - Should not be better accounted for by a preexisting neurocognitive disorder (A minor change from a change in cognition or the development of a perceptual disturbance that is not better accounted for by a preexisting, established or evolving dementia.)
- C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition (no change from DSM IV).
- D. The disturbance develops over a short period of time (usually hours to a few days) and tends to fluctuate in severity during the course of a day (no change from DSM IV)."

The post-operative timing of the onset of delirium is used as the primary clinical differentiator in determining whether a patient is suffering from post-operative delirium or emergence delirium [5]. Since ED is associated with emergence from anesthesia, it typically occurs in the OR and PACU. In contrast, POD can persist for several days after surgery.

Post-Operative Delirium Risk Factors

Delirium seems to result from the interaction between pre-operative patient vulnerabilities and exposure to precipitating factors [6].

POD is frequently observed in elderly patients undergoing orthopedic surgery, particularly hip fracture repair. It most often occurs between postoperative days 1-3 and usually resolves within hours to days [5,7]. Incidence rates fluctuate from 6% in total knee arthroplasty (TKA) to 16% in total hip arthroplasty (THA) [8]. POD appears more frequently following orthopedic surgery for traumatic injuries than after elective surgeries [9,10].

A growing interest in studying pathophysiology of postoperative delirium identified multiple risk factors in elderly patients undergoing orthopedic surgery. A higher incidence of POD was associated with poor post-operative pain control [8,11]. Other proposed risk factors include age, the male gender, number of comorbidities, lower body mass index (BMI) following unintentional weight loss, impaired hearing and vision, pre-operative cognitive decline, depression, alcohol use and pre-operative benzodiazepine administration [12,13]. Dementia free elderly patients who suffered from pre-existing chronic obstructive sleep apnea exhibited an increased POD incidence following a TKA procedure [14].

In patients with pre-existing dementia, a longer emergency department (you already use ED to mean emergence delirium) waiting time and ICU length of stay were also associated with an increased incidence of POD [15]. The sleep-wake cycle is frequently disrupted in delirium. The pineal hormone melatonin is essential in the regulation of the sleep-wake cycle. Studies using polysomnography have demonstrated extensive sleep impairment in ICU patients, with mostly stage 1 and 2 sleep and little to no stage 3, 4 or rapid eye movement (REM) sleep, decreased REM periods and sleep fragmentation [16]. A lower delirium rate was reported in patients receiving melatonin 5mg two times before intervention compared with controls [17].

Emergence Delirium Risk Factors

Emergence delirium (ED) is known as an acute agitation and confusion occurring during or immediately following emergence from general anesthesia, in the OR or post anesthesia care unit (PACU) [15]. Most research on ED involves the pediatric population. However, ED is also seen in adults and is associated with breast, abdominal and musculoskeletal surgery [18,19]. Emergence delirium was studied as a phenomenon occurring after cessation of general anesthesia and was referred to as a general excitation. Silverstein considers postoperative delirium as "a specific subset of the panorama of deliria, consistent with the classical definition of delirium." Emergence delirium should be considered as an independent, separate syndrome due, in part, to its extremely limited duration. A research study involving veterans has identified anxiety, PTSD and depression as risk factors for emergence delirium [20]. Inhalational anesthesia compared to total intravenous anesthesia (TIVA) has also been associated with an increased incidence of ED [21]. Similarly, pre-operative benzodiazepines, chronic illness and long-term anti-depressant use have all been identified as risk factors for agitation in the PACU [18].

There is evidence that regional anesthesia used in conjunction with general anesthesia is associated with a reduction in acute post-operative confusion in both children and adults immediately following orthopedic surgery [22,23]. In elderly orthopedic surgery patients, a retrospective study identified a reduction in ED incidence when elderly patients were treated with morphine instead of meperidine immediately following hip fracture repair surgeries [11,24]. However, there seems to be a paucity of work examining links between orthopedic surgery and ED in adults.

The relationship between certain drugs and the incidence of ED or POD is difficult to assess considering the lack of an animal model and the multiple medication use in anesthesia protocol. Sieber considered depth of anesthesia as a primary variable when assessing the incidence of postoperative delirium in patient undergoing hip fracture repair [25].

Stress and inflammation are important triggers in the development of delirium [26]. There is evidence of an increase in cortisol level in patients over 60 years of age undergoing hip arthroplasty who experienced delirium [27]. This same study also found that the magnitude of this process was related to an increase in IL-6 and IL-8 compared to pre-operative baseline [27]. Also, C-reactive protein (a part of the acute phase inflammatory response) has been associated with dementia in the elderly [28]. Specifically, Beloosesky et al found evidence of increased C-reactive protein (CRP) and inflammatory cytokine (IL-6, TNF- α , IL-1RA, IL-10, IL-8) production in elderly patients undergoing hip fracture repair surgery who developed an impaired mental status and complications (including POD) post-operatively [29]. A study done by Liu et al. using a much larger sample size (330 compared to the 94 used by Beloosesky et al) found evidence of a link between elevated serum interleukin-6 and POD in elderly patients undergoing non-cardiac surgery, 119 of whom were undergoing bone and joint surgery [30]. Patients experiencing POD had a mean post-operative IL-6 serum level of 31.7 pg/ml compared to 23.7 in non-delirious patients ($p = 0.001$) [30]. However, more research is necessary to elucidate the exact mechanism of this proposed etiology in elderly patients experiencing POD.

ED seems to be more associated with arousal and excitation. There is a link between inhalational anesthesia and pre-operative benzodiazepine use in adults experiencing ED [18,31]. Qualitative research by military nursing staff has anecdotally identified a relationship between traumatic brain injury (TBI), post-traumatic stress disorder (PTSD) and hyperactive anesthesia emergence (ED) [32]. This relationship was backed up in research study, confirming an association between pre-operative anxiety, PTSD and ED in military personnel [20]. Pre-operative benzodiazepine administration is associated with ED in the general adult population [31]. Perhaps the association of benzodiazepine use with ED is incidental, and ED has a stronger relationship to anxiety than to anxiolytics.

Increased incidence of ED was also associated with inhalational anesthetic use than when compared to TIVA [21,33]. Experimental evidence from mice suggests that this is due to the excitatory response elicited by these drugs [33]. In this experiment, sevoflurane (an inhalational anesthetic associated with ED) was shown to excite the locus coeruleus neurons (an area involved in adrenergic excitation) in the brains of rats, suggesting that the excitatory properties of some anesthetic drugs are involved in the etiology of ED [33].

Since ED and POD seem to be studied in different populations - ED mostly in pediatric population and POD in elderly patients - a presumed common etiology would require further research to link the two phenomena. An accurate differentiation of delirium from other contributing factors requires a complex analysis of symptoms involved in acute emergence-associated disturbed behavior. Delirium syndromes such as ED and POD present as a heterogeneous mix of symptoms, risk factors and etiologies. Its relationship to central neurotransmitter imbalance has prompted several hypotheses regarding its' association with genetic risk, the

cholinergic system and inflammatory reaction associated with biomarkers release.

Geriatric population represents more than 15% of U.S population and advanced age requires emergency and elective orthopaedic surgery in order to maintain independence. The long term effects of surgery and anesthesia on patients' cognition still remain unclear requiring further investigation.

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