



Peri-operative Cognitive Alterations and the Ageing Brain

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Abstract

Although uncertainties still remain about perioperative neuro-cognitive alterations, emerging literature proves promising regarding our understanding of this brain derangement. The malfunctioning aged Blood Brain Barrier (BBB) combined with the excessive neuro-inflammation hold the key role to neuro-cognitive deterioration. A β and Tau proteins may be effective biomarkers of postoperative cognitive dysfunction in elderly patients. Based on “perioperative cognitive trajectory” combined with geriatric syndrome known as “frailty” it seems quite reasonable to accept the postoperative cognition status as an example of a post hoc ergo propter hoc misattribution fallacy. Although future researches seem mandatory, most researchers suggest that we should focus on the improvement of patients’ peri-operative overall health as this could prevent the deterioration simultaneously with the improvement in patients’ cognition.

Keywords: Peri-operative cognition; Neurodegenerative disease; Frailty; Oxidative stress; Inflammation

Introduction

Nowadays older patients, that previously would not have been candidates for surgery, may undergo operation due to the significant medical progress. Evidences support that acute (40% to 80% incidence) and long-term (10% to 15%) cognitive dysfunction of the ageing brain, are among the most severe complications peri-operatively, often indicating the end of an independent life [1-8]. The aforementioned deterioration may have several forms (postoperative cognitive dysfunction, dementia, Alzheimer’s disease) characterized by deterioration in thinking and perception. By 2050 19 million people, compared to 10 million nowadays, will be facing this potential risk [2,7].

Despite the lack of high level evidences, emerging literature provides quite promising as far as the mechanism of this age-related alteration is concerned. Moving-on from the “peri-operative cognitive trajectory” to the “frailty” syndrome, this serious and highly prevalent complication of ageing society seems to be a post hoc ergo propter hoc misattribution fallacy [2,4].

Reactive oxygen species

Emerging evidences support the thesis of the bidirectional communication between the brain and the immune system and the reaction of the ageing brain to the peri-operative stress becomes more understood [9-15]. The malfunctioning aged Blood-Brain Barrier (BBB) combined with the excessive neuro-inflammation hold the key role to neuro-cognitive deterioration, while the Reactive Oxygen Species (ROS) exasperate the resulting cognitive deficiency [12,16].

Surgical procedure itself activates the Central Nervous System (CNS) immune system which becomes the primary source of reactive oxygen species [9,11,17,18]. Elderly brain is the organ with the most oxygen consumption, the fewer antagonists to oxidative stress and the highest intracellular concentrations of transition metals, catalyzing the formation of ROS [9,11,13,19]. The highest metabolic rate, the predominance of fatty acids, the tendency to peroxidation and the low levels of antioxidants makes the brain the most vulnerable organ to oxidative stress [9,20].

The predominant oxidative environment and the elevated ROS’ levels are capable of modifying nucleic acids, proteins and lipids. The presence of unsaturated fatty acids brain neurons located in the hippocampus is the most sensitive to oxidative stress. The deficiency of enzymatic and non-enzymatic antioxidants, the depleted antioxidants and the markers of oxidative damage make CNS neurons more susceptible to the attack of free radicals. All of the above are implicated in the pathophysiology of peri-operative cognitive dysfunction of the ageing brain [9-13,19].

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B-amyloid and tau protein

Alzheimer's Disease (AD) the most common cause of dementia (80% prevalence), remains one of the greatest ongoing public concern, with increasing impact on the healthcare landscape. Dementia is defined as a clinical syndrome with progressive decline in two or more cognitive domains, including memory, language, executive, visuospatial function, personality and behavior. AD is a progressive neurodegenerative disease that affects 13% of elderly (>65 years old), for which advancing age is a major risk factor, interacting with the abilities to perform instrumental and/or basic activities of daily living [5,6,21-24]. Although the possible link between anesthetic agents, cognitive dysfunction, and Alzheimer disease remains to be clarified, over the past years several studies have accounted for the close relationship between anesthesia/surgery and AD [5-6,16].

B-amyloid peptide plaques and tau protein neurofibrillary tangles, the hallmark pathophysiology of Alzheimer's Disease (AD), are responsible for a cascade of events resulting in cognitive deterioration [6,16,22,23]. Animal studies suggest that some anesthetic drugs impair the metabolism of the aforementioned proteins in the elderly, resulting in postoperative cognitive dysfunction [16,25]. More specifically, the response of the aged brain to general anaesthesia is similar to the molecular changes, including mitochondrial damage, 5 neuronal dysfunction and apoptosis, which are responsible for a progression of pre-existent AD, affecting memory, attention and spatial learning ability [5,6,16,23].

The surgery promotes inflammatory response, which seems to promote the AD pathogenesis; their common denominator seems to be neuro-inflammation. The attempt to relate anesthesia to AD development and vice versa should be based on evidences between exposure and pathophysiological mechanisms underlying the disease. That is to say, A β and Tau proteins may be effective biomarkers of POCD in elderly patients [25]. Finally, is of paramount importance to diagnose both dementia and peri-operative cognitive alterations as early as possible in order to decrease their incidence postoperatively.

Frailty and cognition

Frailty is a multidimensional geriatric syndrome that mostly affects the elderly. It is characterized by cumulative declines of the majority of physiological systems, decreased reserve, and resistance to stressors and vulnerability to adverse outcomes [26-29]. It has a critical role in the peri-operative period and has been recognized as an independent risk factor for adverse outcomes in older patient peri-operatively [26-29].

Cumulative declines of the majority of physiological systems, decreased reserve, resistance to stressors and vulnerability to adverse outcomes constitute the syndrome generally defined as frailty [1,26,27]. Long before identified as a biological syndrome, frailty was equivalent to advanced old age, disability and comorbidity [26]. Currently it has been well-established that the aged are most at risk for postoperative adverse neurocognitive outcomes and that preoperative cognitive impairment is the leading risk factor for postoperative cognitive alterations. All the above considered, it seems that the "brain reserve hypothesis" -lower preoperative scores in cognitive tests and fewer years of education constitute independent and non-modifiable risk factors for postoperative cognitive dysfunction is being confirmed [4,29-36].

Current research suggest that frailty syndrome should be one of the main components of the optimal pre-operative evaluation in

geriatric patients [1,4,26,27]. Frailty is diagnosed by exploring the presence or absence of signs or symptoms including weight loss, exhaustion, sedentary behavior, slow gait and low muscle strength [1,26]. Patients in whom one or 2 of these five criteria (prevalence 45%) are present, are diagnosed with pre-physical frailty, while those in whom three or more are present (prevalence 10%) with physical frailty [1,4,26].

Additionally, cognitive impairment is considered a component of frailty and their association has been investigated worldwide. Based on the significant link between physical frailty and cognitive impairment as demonstrated by several studies, the term cognitive frailty was proposed [29,37,38]. Cognitive frailty is defined by the simultaneous presence of both physical frailty and cognitive impairment in older individuals without definite diagnosis of dementia [28,29]. The prevalence of cognitive frailty remains low (1.0% to 1.8%) and although it appears to be associated with high scores of mortality and morbidity, very few studies have evaluated its exact impact [28].

That is to say, frailty should be considered either as a pre-disability syndrome or as a reversible biological condition [1,26-28]. The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) and American Geriatrics Society (AGS) guidelines for the preoperative assessment of the geriatric surgical patient recommend evaluation of the patient for frailty syndrome according to phenotype model or by testing cognitive, functional and nutritional status, history of falls, comorbidity and anaemia along with the documentation of its magnitude [26]. By doing so, frailty assessment is expected to be a valuable predictive tool for postoperative severe morbidity and mortality, including hospitalization, institutionalization and cognitive alterations moving on to the "patient-centric care" era [1,26-28].

Quality of life

Peri-operative cognitive deterioration is a significant risk factor for lifelong cognitive decline, associated with increased morbidity and mortality, affecting multiple aspects of patients' quality of life. Although, often under-diagnosed, it has important clinical short- and long-term consequences and may lead to lifelong mild cognitive impairment or dementia [2,3,14,31,33,35,39-48]. Thus, early diagnosis and prevention of these peri-operative cognitive disorders should be a standard care step in everyday clinical practice [18].

Individuals with peri-operative neuro-cognitive decline are experiencing an increased duration of hospital stay (2 to 5 days), an impaired period of postoperative recovery and prolonged period of rehabilitation. Moreover, there is a 3-fold increase in the risk of post-discharge institutionalization and the level of care dependence after discharge, with a significant impact on the patient itself, their family and the healthcare burden in the community [2,3,17,31,33,42-45,49-53]. The premature departure from the workforce, the impact on social relationships and the decreased sexual interest or performance, all are of paramount value for an acceptable everyday life quality and should be forewarned preoperatively along with the numerous other risks of preoperative care [14,44,54]. Furthermore, the risk of major complications (including urinary incontinence, falls, decubitus ulcers, cardiac arrest, ventricular tachycardia or fibrillation, myocardial infarction, pulmonary oedema, pulmonary embolus, bacterial pneumonia, respiratory failure requiring intubation, renal failure requiring dialysis and stroke) rises 2 to 5-fold [14,31,34,40,42,55-57].

When it comes to elderly patient's peri-operative neuro-cognitive

dysfunction usually co-exists with increased physical frailty. The aforementioned combination is associated with an increased incidence of adverse outcomes and beyond any question frailty has the capacity to predict the risk of negative health outcomes during a 3-year follow-up period. Older patients face significant impairments in daily functioning such as falls, disability, fractures, hospitalization, and institutionalization, with potentially complete loss of independence [14,28,33]. Regarding the mortality, in a 5-year prospective study cognitive impairment with frailty have been associated with the highest mortality [28]. Last but not least, it should be highlighted that when physical and cognitive frailty are combined with neuro-inflammation clinical evidences suggest that the levels of HMGB1 cytokine after surgery are predictive of the degree of short and long-term post-surgery inflammation and morbidity [11,28].

Conclusion

It seems that there is a strong association between anesthesia and peri-operative neuro-cognitive disorders in older patients. Excessive neuro-inflammation combined with the oxidative processes activation peri-operatively seems to have a key role in the pathogenesis of cognitive deterioration and although uncertainties still remain, cognitive frailty assessment seems to be a valuable tool peri-operatively. The peri-operative cognitive dysfunction as a failure of resilience in the face of peri-operative stress, improved peri-operative care combined with the optimization of physical and functional status of our patients, along with increased training of staff involved in the peri-operative care seems mandatory in an attempt to reduce the incidence of peri-operative neuro-cognitive dysfunction.

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