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Acute peri-operative neurocognitive disorders: a narrative review

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Summary

Peri-operative neurocognitive disorders are the most common complication experienced by older individuals undergoing anaesthesia and surgery. Peri-operative neurocognitive disorders, particularly postoperative delirium, result in long-term poor outcomes including death, dementia, loss of independence and poor cognitive and functional outcomes. Recent changes to the nomenclature of these disorders aims to align peri-operative neurocognitive disorders with cognitive disorders in the community, with consistent definitions and clinical diagnosis. Possible mechanisms include

undiagnosed neurodegenerative disease, inflammation and resulting neuroinflammation, neuronal damage and comorbid systemic disease. Pre-operative frailty represents a significant risk for poor postoperative outcomes; it is associated with an increase in the incidence of cognitive decline at 3 and 12 months postoperatively. In addition to cognitive decline, frailty is associated with poor functional outcomes following elective non-cardiac surgery. It was recently shown that 29% of frail patients died or experienced institutionalisation or new disability within 90 days of major elective surgery. Identification of vulnerable patients prior to undergoing surgery and anaesthesia is the key to preventing peri-operative neurocognitive disorders. Current approaches include pre-operative delirium and cognitive screening, blood biomarker analysis, intra-operative management that may reduce the incidence of postoperative delirium such as lighter anaesthesia using processed electroencephalography devices and introduction of guidelines which may reduce or prevent delirium and postoperative neurocognitive disorders. This review will address these issues and advocate for an approach to care for older peri-operative patients which starts in the community and continues throughout the pre-operative, intra-operative, postoperative and post-discharge phases of care management, involving multidisciplinary medical teams, as well as family and caregivers wherever possible.

Introduction

Peri-operative neurocognitive disorders are the most common complication experienced by older individuals undergoing anaesthesia and surgery. Unlike the research diagnosis of postoperative cognitive dysfunction, peri-operative neurocognitive disorders are patient-centred outcomes and include symptomatic and functional impacts. Peri-operative neurocognitive disorders include: mild and major neurocognitive disorder pre-operatively; postoperative delirium; delayed neurocognitive recovery to 30 days; and postoperative mild and major neurocognitive disorder up to 12 months but which may continue beyond 12 months.[1] Neurocognitive disorders, delirium and postoperative neurocognitive disorders are associated with long-term cognitive and functional decline, increased morbidity and mortality, decreased independence and an increased risk of dementia.[2] These poor outcomes impose an enormous economic and social burden on society, with delirium estimated to cost approximately £32,234 ($43,924; €37,996) per patient, per year, in the USA, and severe delirium as much as £41,100 ($56,006; €48,443) per patient, per year.[3]

Peri-operative neurocognitive disorders are common, occurring in up to 65% of older individuals undergoing surgery and anaesthesia [4]. Critically, as the population ages and surgery is provided to more and more people, an ever increasing number of people aged > 65 y are exposed to the risk of neurocognitive complications. In fact, although those aged > 65 y make up approximately 16.5% of the population in the USA [5], it has been estimated that 53% of all general anaesthetics are administered to this age group.[6]

Despite a plethora of literature investigating adverse neurocognitive outcomes, there remains significant heterogeneity in definitions and criteria for decline. As a result we cannot be sure of the true incidence of cognitive disorders associated with cardiac and non-cardiac surgery and anaesthesia in any individual circumstance, although data for delirium are a little more specific. Nor can we be sure how much of the observed neurocognitive disorders occur in addition to otherwise un-noticed ongoing clinical decline.

This narrative review will consider the clinical and practical implications of peri-operative neurocognitive disorder on patients, and possible pathways for identifying at-risk individuals and assessment of modifiable factors. It will focus on peri-operative neurocognitive disorder and only discuss delirium when directly relevant, as delirium is a substantial problem and is being addressed in a separate review in this issue of *Anaesthesia* [7]. We will consider the recent nomenclature recommendations and discuss the impact of peri-operative neurocognitive disorder on patients and how this influences what we should be telling patients and families. We conducted electronic searches of the literature using PubMed and Medline in July 2021. Limits were placed to include only manuscripts published in English. The authors' own files provided further articles for inclusion in the review. Terms searched included postoperative cognitive dysfunction/decline/impairment/deficit/change; cardiac surgery; non-cardiac surgery; peri-operative neurocognitive disorders. Although we did not include a time limit, we only included what we considered seminal manuscripts prior to 2010, in order to focus on the most recent developments in this field.

Nomenclature

Following on from anecdotal reports, a well-designed study by Simpson in 1961 [8], using similar criteria to that used for assessing dementia in the community, investigated the incidence of dementia following anaesthesia and surgery. Criteria for classification of a decline in cognition and function to meet a diagnosis of dementia included an assessment of physical activity, mental ability,

personality and individual characteristics, undertaken at the patients' homes pre-operatively and postoperatively by the lead author. The authors' found no association between exposure to surgery and anaesthesia and progression to dementia. The question of whether anaesthesia and surgery result in cognitive change re-emerged in the 1980s with investigators primarily focused on cardiac surgery patients. [9,10] The first consensus document on assessment of cognitive change was published in 1995 by Murkin et al. [11] This focused on the essential objective neuropsychological assessments that should form part of studies investigating cognitive change associated with anaesthesia and surgery. This led to the term 'postoperative cognitive dysfunction' being widely applied to describe any objective cognitive change observed in the postoperative period. The impact of any cognitive decline on the ability of the individual to perform normal daily activities was not considered, nor was any assessment made of subjective complaints of memory or thinking. The term 'postoperative cognitive dysfunction' thus represented a new research construct and a major shift away from the clinical definitions and terminology used throughout geriatrics, neurology and psychiatry. Despite ongoing anecdotes and sporadic case reports of significant cognitive decline after anaesthesia and surgery, what postoperative cognitive dysfunction actually reflected clinically was unclear and remains unresolved to this day.

A key issue in defining postoperative cognitive dysfunction was determining a threshold for cognitive decline that constituted meaningful change. Investigators used a variety of neuropsychological assessments ranging from a 5-min screening tool such as the mini mental state examination to a large battery of neuropsychological tests taking 60 min or more to complete. Definitions varied from a single point decline in mini mental state examination to complex calculations for the reliable change index, with some comparing change in surgical patients from baseline, some to a control group, and others relying on normative data. Enormous variations in measurement, definitions and criteria have resulted in significant differences in the incidence of cognitive disorders between studies and have made non-heterogeneous systematic reviews and meta-analyses almost impossible.

Acknowledging the limitations of inconsistent definitions and tests, the International Nomenclature Consensus Working Group was formed and published revised definitions [12]. These allowed the cognitive impairment and decline (including delirium) associated with the peri-operative period (previously termed 'postoperative cognitive dysfunction' or 'POCD') to be interpreted and diagnosed in accordance with DSM defined neurocognitive disorders [13], or mild cognitive impairment [14] and dementia. [15] Importantly, in revising the nomenclature, peri-operative neurocognitive

disorders which had previously been identified only as research constructs, now had direct clinical implications enabling them to be considered in the overall healthcare of the individual. Moreover, since the prevalence of neurocognitive disorders is common in the older community, the terminology after anaesthesia and surgery now aligns with the terminology used in the community setting. This represents a critical achievement to the holistic care of ageing individuals across their lifespan.

Possible mechanisms

Despite numerous published studies across many possible mechanistic models, the pathophysiology of peri-operative neurocognitive disorders remains elusive. Pre-clinical work has directed attention toward the possibility of an association between the pathophysiology of Alzheimer's disease and that associated with anaesthesia and surgery, but this has not translated well to humans. It is also difficult to interpret what represents an equivalent to peri-operative neurocognitive disorders in animal models. In the following section we will address the most likely pathophysiology toward which most current research is directed. The foremost proposed pathophysiology for peri-operative neurocognitive disorder includes neuroinflammation, unmasking of underling neurodegenerative disease and vascular disorders.[16] This is supported by peri-operative complications being associated with inflammation, longer term mortality, disability and cognitive impairment. [17] Other, or additional, mechanisms may include neurovascular events such as covert strokes. [18]

Neurodegenerative disease

Preclinical studies including in vitro and animal models have made critical contributions to our understanding of the possible pathophysiological mechanisms of peri-operative neurocognitive disorder. In particular, mammalian (rodent) models have improved our understanding of potential biomarkers to inform possible mechanisms. Although, there is much rodent research investigating the neurotoxicity of anaesthetic agents on young animals, this review will focus on aged and transgenic animal studies investigating the effect of anaesthesia and surgery on models of peri-operative neurocognitive disorder-like conditions. The initial breakthrough in animal models of peri-operative neurocognitive disorder was the demonstration that volatile anaesthetics were associated with the hallmark pathophysiology of Alzheimer's disease: amyloidopathy and tauopathy. [19] Animal studies have demonstrated little effect on behavioural outcomes of anaesthesia alone, but significant histopathological and biochemical evidence of surgically induced neuroinflammation which is associated with a greater decline in behaviour. [20] Neuroinflammation is thought to be closely linked to peri-operative neurocognitive disorders [21,22], particularly in combination with

vulnerabilities such as increasing age, comorbid disease and genetic factors. Unfortunately, similar to clinical research, preclinical research is hampered by considerable inconsistency in study design and terminology.

Inflammation

Surgery is associated with a significant systemic inflammatory response, although the exact time sequence of this response varies between different markers and remains to be elucidated. There is plausible evidence that peripheral inflammation results in neuroinflammation [23], especially in vulnerable individuals, and that this inflammation is a key factor in triggering a cascade of neurocognitive change. The physiological process of ageing increases levels of pro-inflammatory markers [24], related in part to a decreased ability to suppress inflammation, a process coined 'neuroinflammaging' [25] or 'immunosenescence and inflammaging' (Fig 1) [26]. This is also associated with age-related neurodegenerative disease such as Parkinson's disease and Alzheimer's disease.

Low-grade, chronic inflammation in the elderly increases the vulnerability of the aged brain to external insults.[27] As a consequence of constantly primed microglia, adverse responses to the occurrence of an acute inflammatory episode such as infection, major illness or anaesthesia and surgery may be exaggerated. Thus, in the diseased brain, systemic inflammation leads to an exaggerated inflammatory response resulting in increased neurodegeneration. Recent work by Danielson et al. demonstrated the time-course of cerebrospinal fluid inflammatory biomarkers collected sequentially throughout the peri-operative period were different for those patients who went on to experience cognitive decline at 3 months when compared with those who did not. A similar pattern was not observed in blood derived samples collected at the same time-points. [28]

Neuronal damage

Markers of neuronal damage have been observed in several neurodegenerative diseases, including multiple sclerosis and Alzheimer's disease, and are thought to represent a downstream effect of neuroinflammation and the underlying degenerative condition. The neuronal proteins neurofilament light and tau are released to plasma in response to acute neuronal injury, including acute brain trauma and concussion, as well as acute ischaemia, where the degree of neurofilament light increase correlates with the severity of injury and subsequent adverse clinical outcome. [29] This is analogous to the release of the troponins after myocardial infarction that correlates with degree of damage to myocardial cells. [30]

Blood neurofilament light levels reflect axonal injury [31] and are linked to several neurological pathologies. These include traumatic brain injury [32], supranuclear palsy [33], HIV [34] and multiple sclerosis [35].

Tau proteins belong to the family of microtubule-associated proteins. They are mainly expressed in neurons where they play an important role in the assembly of tubulin monomers into microtubules to constitute the neuronal microtubules network. [26] Microtubules are involved in maintaining the cell shape and serve to guide axonal transport. Tau proteins are the major constituents of intraneuronal and glial fibrillar lesions described in Alzheimer's disease and numerous neurodegenerative disorders referred to as 'tauopathies'. The pathway leading from soluble and monomeric to hyperphosphorylated, insoluble and filamentous tau protein is at the centre of many tauopathies. Planel et al. showed that anaesthesia induced hypothermia could lead to tau hyperphosphorylation in a mouse model [36] and more recently Le Freche et al. showed that immediately after exposure to sevoflurane, phosphorylated tau was increased in the brain. [37]

Frailty

Frailty is reflected by an individual's reduced capacity to recover from a stressful event, increasing the risk of poor outcomes.[38] There are two main frailty paradigms: the frailty phenotype model as proposed by Fried et al. [39] and the cumulative deficit model.[40]

Frailty occurs in up to 37% of community-dwelling older adults and is increasingly used as a predictor of poor outcomes following a stressful event (e.g. anaesthesia and surgery) in older adults.[41] Frailty prevalence increases exponentially with age, with < 10% of community dwelling 65 year-olds classified as frail rising to > 50% of those aged > 85 y.[42] Despite the strong association between age and frailty, frailty itself is a stronger predictor of poor outcome than chronological age.[38] Frailty has been associated with poor postoperative outcomes including increased risk of 30-day mortality, length of stay, delirium and risk of institutionalisation.[43] Recent work demonstrates that pre-operative frailty is associated with an increase in the incidence of cognitive decline at 3 and 12 months postoperatively.[25] In addition to cognitive decline, frailty is associated with poor functional outcomes following elective non-cardiac surgery. Recent work by McIsaac et al. demonstrated 29% of frail patients died or experienced institutionalisation or new disability within 90 days of major elective surgery.[44] It is important to note that frailty does not only impact

outcomes following major surgery, but puts patients at risk for poor outcomes following low-risk procedures as well. [45]

Patient impact

A recent editorial reported that 65% of patients undergoing general anaesthesia in Australia were 'fearful' or 'very fearful' of permanent cognitive deficits after their procedure. [46] Given the high prevalence of peri-operative neurocognitive disorder this is not surprising. Interestingly, the survey group were young and not representative of the population most at risk of peri-operative neurocognitive disorder, suggesting the rate of concern may well be higher in the at-risk, vulnerable older population, especially those who are already experiencing some decline in cognition or function.

Studies investigating postoperative neurocognitive disorder have demonstrated an increased risk of mortality and dementia, a decreased return to the workforce and an increased reliance on social security in those experiencing postoperative neurocognitive disorders at 3 or 12 months following non-cardiac and cardiac surgery. [47,48] The prevalence of dementia 7.5 years following cardiac surgery is also significantly higher in those who experienced postoperative neurocognitive disorder at 12 months following cardiac surgery. [48]

In a longitudinal follow-up of the Whitehall II study by Krause et al., the risk of serious cognitive decline was doubled compared with those who had not undergone surgery.[49]

The consequences of delirium are described below in terms of long-term poor outcomes, and elsewhere in this issue of *Anaesthesia* is a further article highlighting how significant delirium is and includes negative impacts on cognitive and non-cognitive outcomes including mortality.[7]

Prevention/identifying at-risk patients

Non-pharmacological interventions

The *Lancet* Commission on dementia, advocates prevention as the only currently accessible intervention to reduce delirium and dementia. [50] Within the Commission's prevention, intervention and care framework, 10 key messages for dementia prevention are identified and include modifiable risk factors associated with the peri-operative period, including management of risk factors for cardiovascular disease which is closely linked to cognitive decline.

It is now well established that postoperative neurocognitive disorder is more common following an episode of delirium [51], suggesting delirium may be an effective target of prevention programmes. For example, work by the multidisciplinary Sixth Perioperative Quality Initiative (POQI-6) [52] consensus conference recommended multi-component interventions to prevent delirium as a way to reduce longer term peri-operative neurocognitive disorder and other adverse outcomes.[53]

The importance of delirium prevention is demonstrated by estimates that delirium contributes as much as 11% to the overall social burden of dementia. [50,54,55] In older individuals, surgery and anaesthesia result in high rates of peri-operative neurocognitive disorder, including delirium affecting up to 65% of patients [4], new mild cognitive impairment in more than 20% [56] and worsening dementia in up to 30% of patients [57]. The exact association between delirium and postoperative neurocognitive disorders remains unclear, but it is likely that progression along this pathway is not always predictable, and adverse central nervous system events such as peri-operative neurocognitive disorder are avoidable precipitants of further decline. Without clear assessment for delirium, many patients with hypoactive delirium may have been classified as postoperative cognitive dysfunction when assessed in the early postoperative period.

The combination of the large numbers of elderly presenting for anaesthesia and surgery, the high incidence of peri-operative neurocognitive disorder, the significance of anaesthesia and surgery as a risk factor for dementia and the opportunity to implement modifiable interventions make the peri-operative period a unique situation in which to intervene with strategies to prevent and reduce dementia.

With no current prospect of pharmacological treatment, attention has been turned to modifiable risk factors. Several key modifiable risk-factors have been identified (diabetes; hypertension; obesity; smoking; depression; cognitive inactivity and physical inactivity) which account for approximately 50% of all Alzheimer's disease diagnoses. [58,59]

A search of the clinicaltrials.gov and ANZCTR websites suggest there are two studies currently investigating a multi-component intervention to reduce delirium. One study (NCT04857125) proposes to investigate pre-, intra- and postoperative (during admission) optimisation strategies and follows patients for 30 days. Another (ACTRN12619001778178) investigates a broad range of interventions commencing up to 2 weeks prior to surgery and continuing for 3 months postoperatively. Follow-up to 12 months will enable a definitive assessment on any association

between reduction of delirium and longer-term cognitive and functional decline and dementia. The recent Lancet report highlights several factors associated with a risk reduction for dementia which reflect prehabilitation and rehabilitation strategies targeted by these trials, including optimisation strategies, improved management of comorbid conditions, medication management and exercise.[50]

Biomarkers

Recent work by Casey et al. suggests neuronal injury and inflammation are key pathogenic steps in the evolution of delirium.[60] Peri-operative measurements demonstrate blood–brain barrier breakdown as an important pathogenic contributor to delirium.[61] Other indirect evidence to support this hypothesis is accumulating from plasma biomarkers.

Further research of biomarkers of inflammation and neuronal injury (see Inflammation and neuronal injury section above) will help inform pathophysiology and contribute to algorithms to allow early identification of at-risk patients and implementation of appropriate strategies to prevent long term cognitive and functional decline, increased disability, increased institutionalisation and increased morbidity and mortality. Additionally, it is essential to include sequential sampling throughout the peri-operative period, as we have demonstrated the variability in peak trajectories of different biomarkers.[62]

Processed electroencephalography

Various forms of processed electroencephalography (pEEG) such as bispectral index (BIS) monitors (Medtronic; Minneapolis, MN, USA), Sedline® (Masimo, Inc.; Irvine, CA, USA) and Entropy® (GE Healthcare; Chicago, IL, USA) are used routinely in anaesthesia practice as 'depth of anaesthesia' monitors. A number of studies have investigated whether BIS-guided anaesthesia is associated with a decreased risk of delirium, compared with routine anaesthesia care or use of targeted end-tidal volatile agent concentrations. The rationale for these investigations is that adopting BIS-guidance results in less anaesthetic drug exposure, 'lighter' anaesthesia and therefore a reduction in the incidence of delirium.[63] Small studies using the BIS monitor as a measure of anaesthetic depth have shown associations between delirium and low BIS values or burst suppression.[64] Recently, the electroencephalography guidance of anaesthesia to alleviate geriatric syndromes (ENGAGES) trial by Wildes et al. investigated minimising anaesthetic administration and minimising EEG suppression during surgical anaesthesia to reduce delirium.[65] Contrary to expectations, the authors found no difference between BIS-guided anaesthesia and routine care on delirium outcomes

(26.0% vs. 23.0%, p = 0.22). This study had several limitations including their comparator of routine care which resulted in very little separation of anaesthetic dose between groups (0.69 vs. 0.80 minimal alveolar concentration), the median time difference between groups with EEG burst suppression was small (7 vs. 13 min) and the mean BIS level was not reported for either group.

The BALANCED delirium sub-study from our group investigated two BIS targets (50 vs. 35) in patients undergoing major non-cardiac surgery and demonstrated a significant decrease in delirium incidence in those randomised to lighter anaesthesia vs. deeper anaesthesia (19% vs. 28%, respectively, p = 0.03). Whilst the effect of anaesthesia depth remains a controversial issue, on balance, there is now increasing evidence that targeting a lighter level of anaesthesia in patients undergoing major non-cardiac surgery reduces the risk of delirium.[2] The BALANCED delirium sub-study also demonstrated a lower incidence of cognitive impairment at 12 months postoperatively in those with BIS target 50 (lighter anaesthesia) using the abbreviated mental test score. Further implications of pEEG in anaesthetic management for other forms of peri-operative neurocognitive disorder such as delayed neurocognitive recovery or neurocognitive disorder at 3 months or later need to be clarified. Whether or not this applies to a specific sub-group of vulnerable older individuals is not yet evident and should be a focus of future work.[16]

What to tell your patients?

Over recent years, several groups have released guidance documents for the management of older individuals undergoing anaesthesia and surgery. These include the American Society of Brain Health Initiative (https://www.asahq.org/brainhealthinitiative), the American Association of Retired People Global Council on Brain Health (https://www.aarp.org/health/brain-health/global-council-on-brain-health) and the Patient Safety Movement Foundation (https://patientsafetymovement.org/clinical/delirium). With peri-operative neurocognitive disorder, and especially delirium, being one of the most frequent complications elderly patients will experience following anaesthesia and surgery there is a need to convey this risk to patients and carers. Informing patients of these risks allows them to make an informed decision about the procedure they are to undergo, be motivated to engage in risk reduction strategies, and therefore be better prepared should they develop delirium or functional cognitive decline.[66]

Several publications address the need for patient management guidelines, some targeting patients who screen negative for cognitive impairment and are thus considered to be functionally and cognitive healthy [67], and some targeting patients already with a diagnosis of dementia.

Without a greater understanding of the pathophysiology of peri-operative neurocognitive disorder and an ability to identify those at risk in the pre-operative period, we are still some way from understanding how best to prevent these complications. As mentioned above, there is some evidence that multi-component interventions have the potential to reduce delirium, which will hopefully also reduce longer-term cognitive and functional decline. Without routine pre-operative cognitive screening in hospitals for those aged > 65 y, our ability to intervene is severely limited, as is our ability to identify patients who do not have capacity to consent.[66] This problem is unlikely to be one which can be rectified by a single medical discipline, but rather requires a multidisciplinary approach including pharmacists, physiotherapists, nurses, families, geriatricians, psychiatrists and primary care physicians to improve peri-operative care. An approach which starts in the community with a primary care physician and continues throughout the pre-operative, intra-operative, postoperative and post-discharge phases of care management, involving family and caregivers wherever possible would be optimal.

Older individuals undergoing anaesthesia and surgery are at risk of cognitive complications and it is critical this information is provided to the patient and their family so that appropriate informed decision-making and planning can occur.

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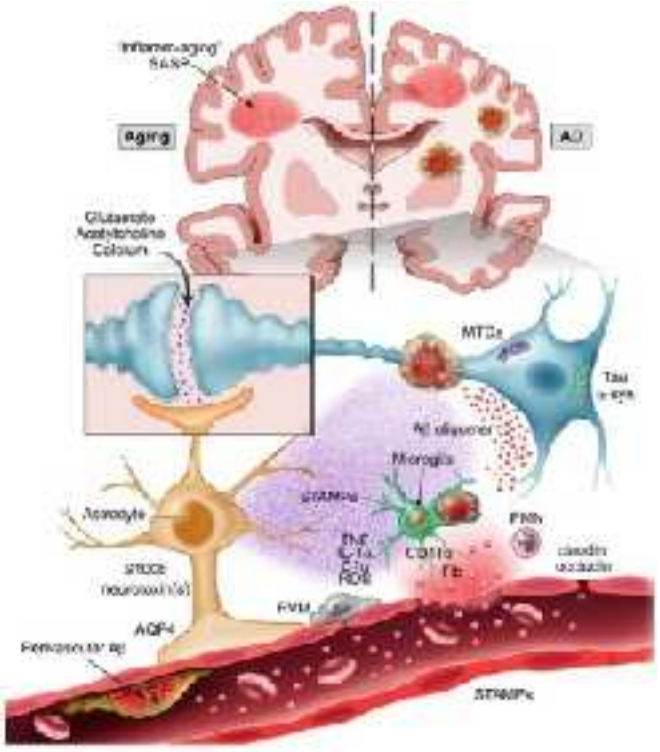
Figure 1. Visual schematic of putative mechanisms involved in the pathogenesis of postoperative delirium. Visual abstract of putative mechanisms involved in the pathogenesis of postoperative delirium. Aging and dementia are the most significant risk factors for delirium. Both states are characterised by chronic inflammation (including inflamm-aging) as well as upregulation of senescent cells (SASP). The Alzheimer's disease (AD) brain has additional hallmarks of vulnerability, pre-existing amyloid β (Aβ) pathology. Together with the classical plaques and tangles, vascular pathology (including perivascular Aβ/cerebral amyloid angiopathy) are commonly found in the AD brain. This ongoing pathology compromises the blood-brain barrier/neurovascular unit (BBB/NVU), which becomes more susceptible to additional stressors like surgery. Surgical trauma associated molecular patterns (STAMPs) can disrupt the BBB and pre-existing BBB pathology amplifies delirium risk in patients. Detailed characterization of STAMPs (including cytokines, damage-associated molecular patterns [DAMPs], resolvins, etc) is needed. A putative factor, fibrinogen, enters the brain parenchyma and activates microglia via CD11b signalling. 'A1' mediators like TNF, IL-1α, and C1q can activate astrocytes contributing to neuronal loss. A similar process may explain postoperative

delirium; however, astrocytes may also be an earlier responder in settings in which the BBB is already compromised. Markers like S100b are detectable at baseline in patients with peri-operative neurocognitive disorders, thus STAMPs affecting astrocytic-end feet, water channels (like AQP-4) and tight junctions (claudin, occludin, etc) may in turn trigger microglial activation. Whether astrocytes directly release specific neurotoxins after surgery that compromise surrounding neurons is unknown. Thus, STAMPs may directly disrupt synaptic plasticity and/or by upregulating other factors like neurotoxic Aβ. These can impair calcium signalling, neurotransmitter release, and induce oxidative stress. Finally, peripheral immune cells may further contribute to this pathology and selective therapies to prevent infiltration may reduce delirium incidence in the vulnerable brain. MTDs, mitochondrial damage associated molecular patterns; PMN, polymorphonuclear leukocytes; ROS, reactive oxygen species; PVM, perivascular macrophage [26].



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