Anesthesia and Alzheimer’s Disease: animal models

FV Marques, TA Lapa, JS Viana, MM Moreira
Centro Hospitalar e Universitário de Coimbra

Abstract
It has been hypothesized that the use of anesthetics agents may enhance the development of Alzheimer’s disease. This dementia affects about 5% of the population older than 65 and is associated with high morbidity. Current evidence suggests a possible association between anesthesia/surgery and long-term cognitive effects. Animal studies suggest an association between anesthesia and neurotoxicity, but this link remains inconclusive in humans.

INTRODUCTION
Alzheimer’s disease is the most common form of dementia. Its worldwide prevalence is estimated to reach 26.6 millions of people and about 5% of those are over the age of 65 [1, 2]. The potential link between memory loss and Alzheimer’s disease to anesthesia is an important preoperative concern from patients and their family members. Postoperative cognitive dysfunction is a well-established perioperative syndrome that arises after a surgical/anesthetic procedure whose exact cause remains unclear[3]. Its incidence varies according to studies, mainly due to the absence of formal diagnostic criteria[4]. How postoperative cognitive dysfunction and Alzheimer’s disease may be linked is an area of research in progress.

MATERIAL AND METHODS
We performed a research on PubMed database of the MeSH terms Alzheimer Disease, Anesthesia, Surgery, Postoperative complications with the inclusion of the most relevant articles.

RESULTS
Alzheimer’s disease
Alzheimer's disease is a progressive dementia that leads to the decline of cognitive abilities. The large majority of cases are of late onset and sporadic in origin. It is a multifactorial disease and is thought to be due to an interaction between genetic and environmental factors [5]. Advancing age is the major risk factor but others, including female gender, family history and specific genetic mutations (apolipoprotein E genotype) can be identified [6, 7]. The disease is characterized by severe neurodegeneration and neuroinflammation associated with progressive cognitive decline [8]. The diagnostic criteria for dementia defines it as the development of cognitive or neuropsychiatric symptoms associated with a decline of previous level of individual performance not better explained by delirium or another psychiatric disorder [9]. Recent guidelines also include biomarker evidence within these diagnostic criteria, such as decreased levels of amyloid-β (Aβ) peptides together with increased total tau protein or phosphorylated tau in cerebrospinal fluid (CSF) [10].

The main disturbance involved in the pathophysiology is the abnormal protein folding, revealing two major hallmarks: 1) senile plaques accumulation, resulting from extracellular Aβ peptide aggregation and 2) intraneuronal neurofibrillary tangles composed by hyperphosphorylated tau protein [11, 12]. The loss of homeostasis of tau protein phosphorylation may result from dysregulation of the kinases and phosphatases involved in this process. The amyloid cascade hypothesis states that the imbalance between production and clearance of Aβ peptides leads to intraneural accumulation [13]. This cascade contemplates that some forms of Aβ peptide are neurotoxic, contributing to abnormal tau phosphorylation. Ultimately this cascade culminates in mitochondrial damage, calcium dysregulation, apoptosis and neurodegeneration [14].

Biomarkers studies show that Aβ peptide concentration in CSF is inversely related to the degree of Alzheimer's disease [15], and tau protein is usually elevated in the CSF of individuals with tauopathies such as Alzheimer disease [16]. The ratio of total tau to Aβ protein is used as a diagnostic adjunct [17].
Animal models
An in vitro study showed that the volatile anesthetics isoflurane and sevoflurane can potentiate oligomerization and cytotoxicity of Aβ peptide [18]. A recent study showed that 2.1% sevoflurane for 6 hours may induce caspase-3 activation and apoptosis, as well as increased Aβ protein levels in the brain tissues of neonatal mice. Furthermore, sevoflurane anesthesia lead to a greater degree of neurotoxicity in the brain tissues of the transgenic mice (Aβ protein precursor mutation), when compared with naïve mice [19]. 12 months-old transgenic and nontransgenic littermate mice were exposed to isoflurane and halothane for 120 minutes a day for 5 days. Transgenic mice were overlaid with Aβ protein plaques after halothane exposure and tau protein aggregation after isoflurane exposure [20]. Using the same mouse model, the animals were exposed to isoflurane 20-30 minutes 2 times a week for 3 months. Transgenic mice showed reduced exploratory behaviour, increased mortality and signs of responses similar to Alzheimer's disease including increased numbers of apoptotic cells, reduced autophagy, reduced astroglia increased microglial response and increased amyloid-β aggregates [21]. The presence of cognitive impairment following surgery is reasonably well established. The postoperative cognitive decline was associated with microgliosis, Aβ peptide production and tau protein hyperphosphorylation in the hippocampus of aged mice [22]. Surgery leads to the production of tumor necrosis factor-α, which subsequently damages the blood-brain barrier, increases inflammatory macrophages infiltration in the hippocampus [22]. The levels of the cytokines interleukin-1β and interleukin-6 have also been shown to increase in mice that underwent surgery, compared to mice that only received anesthesia [23].

DISCUSSION/CONCLUSION
It is important to understand that animal studies are not able to completely separate surgery from anesthesia because the majority of surgical procedure needs anesthesia to be performed. It remains unclear as to the conditions under which anesthetic drugs exposure results in neurodegenerative changes and cognitive impairment. Although animal models have helped to understand some of the mechanisms associated with neuronal loss and accumulation of neurotoxic proteins, the connection between these injuries, symptoms and causes of Alzheimer’s disease remains difficult to uncover. A causal link between anesthetic-induced biochemical markers of neurotoxicity and the establishment of long-term cognitive dysfunction is necessary to build up the proposed relationship between anesthesia and neurodegenerative changes.

REFERENCES
1. Hebert LE, Bienias JL, Aggarwal NT, et al., Change in risk of Alzheimer disease over time, Neurology, 2010; 75(9):786-91.