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EDITORIAL ARTICLE

Playing games with the brain: The possible link between anesthesia and Alzheimer’s disease revisited

Jugando con el cerebro: revisión del posible vínculo entre la anestesia y el Alzheimer

F. A. Lobo a,*, A. P. Saraiva b

a Anesthesiology Department, Hospital Geral de Santo António, Porto, Portugal
b Anesthesiology Department, Hospital Geral de Santo António - Centro Hospitalar do Porto, Porto, Portugal

The brain is the most complex and remarkable organ in the human body: through infinite neuronal synapses and networks, neurotransmitters and neural impulses, the brain establishes in- and out-pathways receiving and sending all kind of information to command and integrating the other organs physiology. This simplistic view of the brain structure and role does not eliminate a question that we must have on our mind: does an organ so sensitive and complex enjoys to be touched and switched off by anesthetic drugs? In other words, do general anesthetic drugs jeopardize some cerebral neuronal circuits function while acting on, changing and turning off consciousness or consciousness-related pathways?

Entities as postoperative cognitive dysfunction (POCD) and postoperative delirium may be seen as early consequences of a disrupted brain function elicited or, at least, with some contribution of anesthesia, anesthetic drugs and/or surgery. Some authors have been extensively reviewing the subject, trying to shed some light on the risk factors, the pathogenic mechanisms leading to a postoperative cognitive decline and, lately, the pathological mechanisms underlying POCD mimicking Alzheimer’s Disease (AD). Curiously, there’s a simultaneous trend among patients towards a fear about perioperative and anesthesia-related brain injury and memory loss, which was already brought to the public attention.

Several comprehensive reviews have been describing the AD which is estimated to affect 26.6 million people and is the most common form of dementia with higher prevalence with increasing age from 65 to 85 years old. The large majority of cases (over 99%) are late onset and sporadic in origin, with multifactorial ethiopathology, with external factors interacting with biological or genetic susceptibility to accelerate the manifestation of the disease. Exposure to anesthesia might be such an external factor and the possibility that anesthesia/surgery may trigger or accelerate a demential process is fearful and deserves a special attention.

A consensus statement coming from the First International Workshop on Anesthetics and AD held in 2008 provided us with an important tool for a comprehensive view of this possible link but 6 years after there are still many unanswered questions. How to look to these puzzled connections between surgery, anesthesia, anesthetic drugs, anesthesia techniques, concurrent perioperative events as hemodynamic and metabolic changes, in vitro-, animals and human studies and cognitive performance before and after surgery/anesthesia: rejecting the worst scenario or accepting that something may exist and search for protective strategies until definite evidence is proved.
Intersection of anesthetic drugs and pathological hallmarks of AD

Amyloid beta (Aβ) and tau protein fibrillar lesions are the classical hallmarks of AD. Briefly, mutations in the amyloid precursor protein (APP) enhance the production of a small series of soluble, unstable proteins called the amyloid-beta, which may undergo a process of association and oligomerization when exceeding some solubility threshold; these small oligomers may produce neuronal and synaptic damage, and its assembly in larger monomers results in senile plaque, the histological hallmark of AD. The other characteristic lesion of AD is the intracellular neurofilibrillary tangle (NFT), composed primary by protein tau, which dephosphorylated form provides stability to microtubules (MT). When tau phosphorylation occurs, the protein detaches from microtubules and becomes cytoplasmatic; an enhanced tau hyperphosphorylation may lead to microtubules disruption but also to tau association with NFTs production.

Several experimental studies have been showing a strong association between anesthetic agents and these molecular pathways of AD. Inhalational agents may increase Aβ production, oligomerization and accumulation, promoting plaque formation in vitro and in vivo, nicely reviewed by Xie and Xu. Potent volatile anesthetic agents also interfere with the phosphorylation, aggregation and function of microtubule-associated tau protein and concomitant cognitive impairment although is unknown if the hyperphosphorylation of tau protein is induced directly by the anesthetic agents or by the anesthesia induced hypothermia or by both.

Calcium metabolism also seems to play some role on AD pathogenesis and again, through this alternative pathway, anesthetic agents may interfere and strengthen neuronal cell damage.

Curiously, intravenous agents as propofol and thiopental are likely to be protective in comparison with the evidence described for potent volatile anesthetic agents, which may be significant for translational research developments.

Too many roads open to nowhere: human studies and absence of evidence

Current clinical studies have failed so far to provide solid evidence that exposure to anesthesia and/or surgery is associated with an increased risk of AD.

Association between early POCD and anesthesia has been well documented in human studies. This cognitive decline is usually transient and reversible, with patients recovering 3–12 months after surgery. However, the acute changes associated with POCD might predispose patients to chronic changes associated with dementia, with a possible bimodal pattern of cognitive decline. When interpreting the clinical evidence of the association between cognitive decline and anesthesia, several barriers arise between our doubts and the scrupulous true. In a recent review, the authors address a number of inconsistencies regarding the design of these studies, such as the methodological issues (diagnosis of early and persistent POCD, learning effect, statistical analysis), the patient-related factors (age, pain, co-morbidities, vulnerability, cognitive trajectory, pathology preceding dementia) and the variety of postoperative outcomes accessed (postoperative events, quality of life, postoperative cognitive trajectory). The number and significance of the possible biases accounting for all of these variables make difficult to interpret the heterogeneous results.

Nevertheless, in the last few years, studies did not find a relationship between surgery, anesthesia or early POCD and dementia. Only one study found that patients, who had undergone CABG surgery under general anesthesia, when compared to patients submitted to percutaneous angioplasty, had a higher risk to develop AD. Biochemical markers of brain damage, neuroinflammation and, importantly, of AD as amyloid-β peptide and tau protein have been found increased after anesthesia and surgery, mainly when inhalational anesthesia was employed with rather intravenous anesthesia with propofol. It should be remarked that desflurane seems to have a different pattern than isoflurane, lowering amyloid amyloid-β peptide in CSF in humans.

Interestingly, there’s also evidence of higher risk of Parkinson’s disease, which has some similar features with AD, among anesthesiologists as compared with internists.

Two recent Taiwanese studies, using the Taiwan’s National Health Insurance Research Database (NHIRD), found an association between anesthesia and diagnosis of AD, independent of the type of surgery, amount of anesthetics used, or cumulative duration of anesthesia; however, there are important limitations as highlighted by Sprung, mainly related with the lack of consistency in diagnostic criteria and the possibility of inaccurate coding that can exist in such a database. A French study found similar results but still lacks scientific validation as a published study.

Whether underlying diseases of patients, hospitalization, surgery-related inflammatory responses or anesthetic management causes POCD or subsequent dementia, also remains unclear. Adding fuel to the fire, there’s an intriguing theory advanced recently suggesting that there is potential for cognitive improvement after surgery, when it improves health, quality-of-life, and decreases inflammation and pain levels.

The present and the future: searching for the patients at risk

In view of conflicting evidence, it is imperative to invest in future studies, based on scrupulous methodology, which can undoubtedly translate the association between anesthesia brain damage and AD from the biological plausibility field to the evidence based medicine. But while more and better-designed studies are being conducted, should we be adventurous and proceed with our eyes wide shut until the defendant is proved guilty as charged? Or should we be judicious and search for some protective strategies for our patients?

Indeed, facing the available literature, we can identify some risk factors concerning the possible development of dementia following surgery and/or anesthesia. There are some well known risk factors for AD including advanced age, female gender, lower educational level, family history, cardiovascular diseases, diabetes mellitus, depression, and
head trauma\textsuperscript{44-45} and cardiac and major orthopedic surgery seem to be those most notably associated with postoperative cognitive decline.\textsuperscript{21,46} But some other possible risk factors deserve our attention: the cognitive trajectory before surgery may be an important determinant of the postoperative dysfunction,\textsuperscript{44} with the postoperative cognitive decline reflecting a pre-existing downward tendency; or the personality trait of our patients, like neuroticism, and conscientiousness, may play an important role as showed by a metaanalysis by Terracciano et al.\textsuperscript{47}

Another non-modifiable factor to consider is genetics. The apolipoprotein E $\varepsilon4$ genotype is an important risk factor for the development of late-onset AD,\textsuperscript{48} although there is conflicting evidence regarding its association with POCD.\textsuperscript{48,49,50} Nevertheless, individuals carrying the $\varepsilon4$ genotype suffering from POCD could be at higher risk of developing AD. Curiously, this genotype is associated also with the occurrence of delirium in ICU\textsuperscript{31} and after non-cardiac surgery\textsuperscript{28} and with higher requirements for propofol for loss of consciousness during general anesthesia induction\textsuperscript{53}; this association with higher anesthetic needs seems to follow with the finding that transgenic AD-mice have been showing to have higher MAC values for volatile agents.\textsuperscript{24}

Pain is another issue to be addressed. It has been shown in neuroimaging studies that patients with chronic pain have a decreased gray matter density in regions like the anterior cingulate cortex, insula and dorsolateral prefrontal cortex, which have an important role in the perception and integration of painful stimuli.\textsuperscript{13,55} We also know that acute pain in the postoperative period can cause delirium and POCD\textsuperscript{57,58} and that acute postoperative pain is a risk factor for the development of chronic pain.\textsuperscript{59} Thus, postoperative non-controlled acute pain could be a risk factor for the development of permanent brain damage and optimal acute pain control and adequate selection of chronic pain patients for major procedures such as spine or joint replacement surgery are mandatory.

As the peri-operative period conveys a series of aggressions to the body homeostasis, the association of surgery/anesthesia and POCD or dementia, could not only be due to the trauma stress response and anesthetics’ toxicity but also to the cumulative effect of small insults like glucose disturbances and insulin dysfunction,\textsuperscript{60} temperature control,\textsuperscript{13,61} blood pressure\textsuperscript{62} and adequate oxygenation.\textsuperscript{63-64}

The present and the future, part 2: how to proceed with the old patient undergoing spine surgery next Monday morning?

Following the open roads described above, we face a conflict: is there any evidence leading us to change our practice in someway or should we continue to use the drugs, anesthetic techniques and routine monitoring strategies we have been using for years?

Regarding the conflicting evidence of the association of anesthesia and AD, as Woehlck did addressing the approach for intraoperative carbon monoxide poisoning prevention,\textsuperscript{65} we may classify the clinical anesthesiologists into three groups: the Overconcerned, the Apathetic and Negativist and the Level-headed. The Overconcerned have been anesthetizing many old patients, have managed many patients with postoperative cognitive disturbance, have heard some relatives of patients saying “Grandma has not been the same since she had anesthesia”, or is just the worrying sort. The Apathetic and Negativist may be overconfident, unimformed or simply is the modern John Henry folk (\url{http://en.wikipedia.org/wiki/John_Henry_(folklore)}) fighting against something that may counteracts all his lifelong practice. The Level-headed anesthesiologist will keep his mind open to the possibility of the association between anesthesia/surgery and AD, but not so much for the brain not to fall out, pursuing the best care of his patients, identifying risk factors and minimizing the deleterious effects of the least worst anesthetic options.

A Level-headed anesthesiologist managing an old hypertensive patient submitted to spine surgery would elaborate an anesthetic plan aiming a tailored anesthesia; in other words, he would choose total intravenous anesthesia, preferably with target-controlled infusion of propofol and remifentanil, avoiding inhalational agents,\textsuperscript{65,66} monitoring the level of consciousness depression using a processed EEG index of consciousness,\textsuperscript{67} having in mind the limitations of these parameters,\textsuperscript{68} and possibly brain oxygenation\textsuperscript{64} and some form of noiceception-anti-noiceception balance monitoring,\textsuperscript{69} controlling tightly the temperature\textsuperscript{64} and glycemia,\textsuperscript{66,70} with a multimodal postoperative analgesic plan including parecoxib.\textsuperscript{71} Even if some of these attitudes in the future will be proved as useless and devoid of evidence-based benefits, the open-minded and Level-headed anesthesiologist cannot be accused today of misuse and redundancy.

We were taught during the last two decades that modern Anesthesiology was reaching the maximum of safety patterns. Now, the possibility of anesthesia and/or surgery promoting or triggering AD development may be seen as a threat for this well-established highly safe and high-quality medical specialty. Some may even throw it into the big bag of medical damned lies (\url{http://www.theatlantic.com/magazine/archive/2010/11/lies-damned-iles-and-medical-science/308269}). By the opposite, we prefer to quote George Bernard Shaw, “All great truths begin as blasphemies”, while hoping for better and proved epidemiological evidence establishing or not a link between anesthetic exposure and the risk of AD.

References

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