

Preface

Anesthetics and Alzheimer's Disease: Background and Research

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Numerous anecdotal reports suggest that elderly subjects undergoing surgical procedures may experience long-term cognitive impairment with clinical features similar to those in patients with dementia, raising concerns that surgery and anesthesia could increase the risk of Alzheimer's disease (AD) or accelerate the progression of the condition [1]. The population of surgical patients is aging and we are thus presently confronted by both increases in the number of persons at risk of developing AD and the number of elderly persons undergoing surgical procedures. Any possible association between the two therefore merits careful consideration.

Central nervous system complications have long been associated with cardiac surgery, where significant cognitive deficits have been observed in a high proportion of patients across a wide range of intellectual abilities weeks to months after the procedure. While the area of cardiac surgery has provided the first assessments of cognitive functioning, it has been difficult to attribute observed changes specifically to anesthesia given the number of likely confounding factors, notably extracorporeal circulation, vascular disease, pain, and stress. Moreover, while preventive pharmacological interventions aiming at cerebral protection have been

repeatedly attempted in relation to cardiac surgery, it has been difficult to decrease the incidence of cognitive decline [2].

New interest in this area has been generated following observations of cognitive decline after non-cardiac surgery, in which the potential role of anesthetics has been highlighted [3,4].

In the last few decades, anesthesia management has clearly shown major advances in technology and drug development, permitting improvement of surgical techniques and the possibility of performing complex, prolonged surgical operations even in the very elderly and the critically ill. As a consequence, the evolution of anesthesia procedures has been considered to be amongst the greatest achievements in medicine.

In the absence of either a single coherent etiological model to explain the cause of AD or an effective treatment, recent research has focused on reduction of disease incidence through identification of risk factors. In this context the question of the association between AD and anesthesia has again been raised [5,6]. Accumulating clinical and epidemiological evidence has pointed to the potential adverse consequences of general anesthesia and a possible link with anesthesia-induced changes in molecules known to be involved in the pathogenesis of AD [7].

With regard to epidemiological evidence, the EURODEM Risk Factors Research Group performed a re-analysis of eight case-control studies exploring several

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medical conditions that had previously been suggested as possible risk factors for AD. Among these, general anesthesia was not associated with AD [8], however, there was considerable variation in data collection methodology and type and duration of anesthesia was not taken into account.

Two years later, the California Alzheimer Disease Diagnostic and Treatment Center Program collected data on a large database of subjects with dementia (502 subjects with vascular dementia and 810 subjects with probable AD) examining differences in risk factors. They discovered that vascular dementia subjects were more likely to have a history of general anesthesia and concluded that general anesthesia is a risk factor for vascular dementia [9]. In 1994, the Bohnen group evaluated prior exposure to general anesthesia as a potential risk factor for AD. No significant difference in mean cumulative exposure (in minutes) to general anesthesia or exposure to six or more episodes of general anesthesia were significantly associated with AD [10]. Similar negative findings have been reported by other groups using neuropsychological testing within both cross-sectional and longitudinal study designs, however, this research has been limited by low statistical power, variability in the quality of cognitive testing, and inadequate data relating to type of surgery, the time interval between surgery and follow-up, and age at exposure to anesthesia [11–13].

Additionally, epidemiological studies have not till date been able to adequately separate out the effects of anesthetics from underlying disease and associated activation of inflammation and other responses [14, 15]. Several research groups are now investigating the neurotoxic effect of anesthetic drugs and combinations of drugs. Experimental findings suggest that certain anesthetic molecules can, in laboratory models, induce changes in protein expression in the brain of animals [16,17]. This research has led to many important findings notably that smaller sized, inhaled anesthetics oligomerize A β peptide [18–21] and increase other proteins which have been shown to play a role in AD [22,23]. AD is a devastating disease. After cancer, Americans fear AD most, but among adults aged 55 and older, the fear of getting AD is greater than the fear of cancer [24]. It is important, however, that such fears do not lead to an irrational rejection of surgery in later life. Surgery and anesthesia have done much to improve both the length and quality of life, so that the question of the relationship of dementia to anesthesia requires careful consideration and future recommendations backed by evidence-based argument. The current

supplemental issue of the *Journal of Alzheimer's Disease* thus hopes to contribute to this ongoing constructive debate.

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