Correspondence

Alzheimer’s disease and anaesthesia

Editor—It was with particular interest that we read the review article by Fodale and colleagues on Alzheimer’s disease (AD) and anaesthesia. In the same month, our department received a letter from the family of an 80-yr-old lady diagnosed 4 yr previously with AD. She had undergone an elective hip replacement in 1998. The patient received a general anaesthetic using isoflurane and the operation, lasting 2 h, was unremarkable. At around this time, the family report that the patient started experiencing increasing problems with her memory. Having read a recent article in the New Scientist titled ‘Alzheimer’s alert over anaesthetics’, in which Mandal is quoted as saying ‘It’s a seriously deadly combination when an older person receives halothane’, the family were inquiring as to whether the volatile anaesthetic administered in 1998 could have lead to the development of the patient’s AD.

Mandal and colleagues have shown experimentally a molecular pathway by which halothane induces structural alterations of the amyloid beta peptide resulting in oligomerization, a risk factor for AD. This interaction of inhaled anaesthetics is also noted in Fodale’s review article. Both Mandal and Fodale acknowledge studies disproving an association between the number of anaesthetics received and the development of AD, but Mandal contends that it is the duration of anaesthesia that is critical for the onset of AD, not the number of anaesthetics.

On review of the evidence to date, Fodale and colleagues concluded that the relationship between general anaesthesia and AD has not yet been clarified. They do, however, acknowledge the potential neurotoxic effects of several anaesthetic agents and suggest that further epidemiological prospective studies are required examining the link between general anaesthesia and AD. Fodale and colleagues also highlight the inhibitory interaction of anaesthetic drugs on central cholinergic transmission in the brain and support the hypothesis linking anaesthetic agents with the pathogenesis of postoperative cognitive dysfunction. Given this emerging knowledge and the ageing population, Fodale and colleagues consider a careful mental state evaluation mandatory for all elderly patients undergoing general anaesthesia. This has potentially huge implications. Just how the mental state evaluation is to be conducted is not clear. The limitations of tests assessing cognitive decline and the misuse of simple test such as the Mini-Mental State Examination have previously been highlighted. Any test introduced must therefore be appropriately validated. Additionally, who would conduct the mental state evaluation? If the anaesthetist, would we receive appropriate training and have sufficient time to conduct the evaluation before operation? What would be the costs involved? Finally, in the climate of empowering patients and informed consent, could have lead to the development of the patient’s AD.

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should we be consenting elderly patient to the risks of postoperative cognitive dysfunction?

A review of the admission clerking of our patient interestingly noted the patient to be ‘a bit forgetful’. Whether a formal mental state evaluation would have indicated our patient as having early cognitive decline, and allowed us to tailor our anaesthetic, we will not know. It does, however, seem likely that this letter may be one of many to come and the excellent review article of Fodale and colleagues, puts us in a stronger position to answer such inquiries.

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Editor—We appreciate the interest expressed by Drs Collyer and Frater in our article, since it gives us another possibility of discussing this intriguing issue. Patients’ acceptance of general anaesthesia is founded on the assumption that its effects are totally reversible. But researchers from many centres have convincingly demonstrated that measurable cognitive dysfunctions, called postoperative cognitive dysfunctions (POCD), are a common complication after anaesthesia.6 Cognitive dysfunctions may manifest both as memory loss and as psychomotor derangement.7

AD is the most common dementia disorder characterized by multiple pathological changes in the brain, leading to a progressive memory loss and other cognitive symptoms producing occupational and social disabilities.8 Genetic evidence, confirmed by neuropathological and biochemical studies, indicates that excessive beta-amyloid protein (Aβ) generated by amyloidogenic processing of the beta-amyloid precursor protein (APP) plays a fundamental role in AD neuropathogenesis. In addition, Aβ clearance and APP adaptor proteins can contribute to AD neuropathogenesis by affecting Aβ levels.9

Current literature suggests the potential involvement of AD neuropathogenesis in POCD.9 Aβ, the major constituent of senile plaques in the brains of patients with AD, is related to the impairment of learning and memory, and neurodegeneration,10 and its continuous infusion results in learning and memory deficits in rats.11 Beta-amyloid directly inhibits human cholinergic α4β2-nicotinic acetylcholine receptors.12 Treatment with Aβ at very low concentrations for 7 days significantly decreased the number of nicotinic receptor binding sites and mRNA levels.8 We know that the central cholinergic system plays a major role in regulation of cognitive functions: agonists of central nicotinic acetylcholine receptors and muscarinic acetylcholine receptors may improve, whereas receptor antagonists impair performance in cognitive tasks. Inhibition also contributes to learning and memory impairment and delirium.13 14

Inhaled anaesthetic agents remain the mainstay for patients undergoing major surgical operations, especially in elderly patients. Clinically, relevant concentrations of isoflurane induce apoptosis, alter APP processing, and increase Aβ production in human cell lines. Because altered processing of APP leading to accumulation of Aβ is a key event in the pathogenesis of AD, these findings may have implications for use of this anaesthetic agent in individuals with excessive levels of cerebral Aβ, and elderly patients at increased risk for postoperative cognitive dysfunction.15 In addition, isoflurane interacts with Aβ40 peptides and promotes Aβ oligomerization and cytotoxicity.16 17

On the basis of his experimental published data, Mandal2 suggested that ‘the inhaled anaesthetics halothane and isoflurane encourage clumping of beta amyloid protein. Halothane interacts directly with a pocket in the beta amyloid protein, changing its shape and encouraging neighbouring proteins to bind. Giving elderly patients certain general anaesthetics could increase their risk of developing Alzheimer’s disease and other memory and attention problems’. Therefore, anaesthesia for elderly patients is considered as a risk factor in AD as they frequently experience deterioration in cognitive function with long exposure to anaesthetics during surgery.3

Previous retrospective studies had concluded that it seems unlikely that multiple exposures to general anaesthesia increase the risk of AD,4 18 but today the knowledge of the pathophysiology of neurodegenerative disorders has been dramatically improved, and now we should keep in mind that anaesthesia drugs are not totally safe.

Drs Collier and Frater rightly suggest that the relationship between general anaesthesia and AD has not yet been clarified, but all these aspects, taken together, open new, intriguing, and maybe challenging, scenarios for our clinical practice. In addition, we should be aware that these findings may have implications for the information given to elderly patients before surgery and, therefore, we should be prepared to answer many inquiries, and possible legal implications, in the near future.

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2 Phillips H. Alzheimer’s alert over anaesthetics. New Scientist 2006; 2575: 12
Correspondence

Coma after combined spinal-epidural anaesthesia

Editor—Although neurological complications due to spinal drainage after regional anaesthesia are very rare,1 we would like to report a patient who had no neurological signs before operation but became comatose after combined spinal-epidural anaesthesia (CSE).

An 82-yr-old female patient was admitted with a right hip fracture. Previous medical history included hypertension for 30 yr, a colostomy 12 yr previously due to colon cancer, and a left hip fracture 6 yr ago. On physical examination, she had poor general status, normal conscious level, and complete orientation. All the routine pre-operative test results were within normal limits other than a raised blood urea of 14 mmol litre−1 and a creatinine of 260 μmol litre−1. Neurological examination was normal. CSE was chosen as the anaesthetic technique and she was informed about the operation. With the patient in the right lateral decubitus position, a 25G needle was inserted at the L2/3 interspace at first attempt, clear cerebrospinal fluid flow was observed, and 1.6 ml bupivacaine 0.5% was given intrathecally, and an epidural catheter inserted. The sensory block rose to T10 and surgery was carried out. She was discharged to the ward after the operation. After an uneventful test dose, postoperative epidural analgesia was maintained with an infusion of bupivacaine 0.125% at 5 ml h−1. On the second postoperative day, the patient became agitated, disoriented, dyspnœic, and tachipnoeic, and was transferred to the intensive care unit. A pulmonary CT discounted pulmonary thromboembolism, but the appearance suggested active infection so sulbactam–ampicillin was started for the presumed diagnosis of aspiration pneumonia. Haloperidol was given for the delirium. There were no pathological changes or localization signs on neurological examination, although confusion developed on the third postoperative day. The patient became comatose and required tracheal intubation on the fifth postoperative day. Cranial MRI showed a 5–6 cm mass in the left frontal lobe suggestive of a meningioma with diffused oedema surrounding it, causing central herniation. After treatment of the oedema, a further MRI scan showed a meningioma with a haemorrhagic component, and diffused oedema and increased middle line shift were observed. The patient did not respond to therapy and died on the 18th postoperative day.

Luvar puncture is contraindicated in patients with raised intracranial pressure because it increases the pressure gradient between supratentorial and infratentorial compartments, thus risking herniation.2 Our patient had no symptoms of increased intracranial pressure before operation. The intracranial mass and herniation were identified on MRI taken after the rapid deterioration in consciousness of the patient. It was thought in this case that the intracranial pressure gradient after CSE anaesthesia caused herniation. Hilt and colleagues3 used epidural catheters for the treatment of pain in patients with increased intracranial pressure, and noted that local anaesthetic solutions given epidurally caused dramatic increases in intracranial pressure. Epidural anaesthesia-related increase in intracranial pressure can be very detrimental, especially in patients who had increased intracranial pressure previously.2–5

Regional anaesthesia techniques are extremely reliable when they are used appropriately, but there is always some risk of complications. In this case, we want to remind others of the possibility of an undiagnosed

9 Fodale V, Santamaria LB. The inhibition of central nicotinic nACh receptors is the possible cause of prolonged cognitive impairment after anesthesia. Anesthesiology 2003; 97: 1207
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