Single or multiple encounters of general anaesthesia do not cause any cognitive dysfunction: Findings from a retrospective population-based, case-control study

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Abstract: General anesthesia and surgery have been associated with acute cognitive impairment in several elderly individuals. Present study was conducted to determine whether the general anaesthesia exposure and cognitive dysfunction are linked or not. This is a China-based retrospective, population-based and case-control study. Using Chinese database inhabitants of Shenyang, China, incident cases detected with cognitive abnormalities between January 2007 and December 2012 were identified. With respective to every incident case, age- and gender-matched control subject was chosen among the general population pool of Shenyang inhabitants who were not having cognitive anomalies in the year. Medical records were scrutinized to examine the exposures to surgical procedures necessitating anesthesia after 45-years of age. We examined 577 cases of cognition-impaired (dementia) patients, every incident case with a conforming control subject. Among the cognitive impaired patients, 414 (71.7%) underwent 821 surgical operations needing general anesthesia exposure; of the controls, 404 (70%) underwent 833 surgical procedures. The present study found that general anaesthetic agents encounter was not markedly associated with cognitive anomalies (odds ratio, 0.87; 95% CI, 0.71-1.09; P=0.29). Moreover, no substantial relation was observed when the anaesthetic agents encounter was measured as number of surgical operations (odds ratios (OR), 0.83, 0.89, and 1.0 for 1, 2-3, and 4 exposures, correspondingly, matched with none; P=0.52). Our present work witnessed no substantial link between surgical procedures requiring single or multiple general anesthesia exposure post 45-years of age and cognitive dysfunction.

Keywords: Anesthesia, dementia, Alzheimer's disease, China, surgery.

INTRODUCTION

Frequent exposures to anesthesia and surgical operations are generally associated with short-lived postoperative memory abnormalities. However, exact mechanism for this observation is not yet well-known (Newman *et al.,* 2007). An important observation is that the resultant cognitive abnormality and dementia from anesthesia exposure might stay for long-term (Newman *et al.,* 2007; Seitz *et al.,* 2011). These properties of anaesthetic agents were established in a set of sequential studies in which animals were challenged to various anaesthetic agents. The neurohistopathologic lesions in the experimental animals were identical to those observed in Alzheimer's disease (AD). A prominent observation was the accrual of β-amyloid in brain and the precipitation of lumps of neurofibrillary tangles (Xie *et al.,* 2007). Impact of anesthesia exposure and its association with cognitive dysfunctions were determined in a few previously reported studies. As concluded in a latest systematic review, there is no substantial relation between the general anesthesia encounters and cognitive abnormality or dementia (Xie *et al.,* 2007). However, the present data emerged from the studies which are having remarkable boundaries, such as sample sizes, selection of proper controls, no data in association to the anesthesia encounters, and stringent use of detection criteria for cognitive impairment. This study is conducted to evade the draw backs of previous studies. This study got approval to access all the medical reports of inhabitants of Shenyang, China which includes all incident cases of cognitive abnormality in Shenyang, China between January 2007 and December 2012 and an age- and gender equal cohort without cognitive dysfunctions at the time of reporting year of diagnosis. The objective of our study is to test the assumption that encounters to the general anaesthetic agents after 45-years of age is non-significantly related with incident cognitive dysfunction using in case-control study design.

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MATERIALS AND METHODS

Methodology

We have performed a retrospective study in a case-controlled fashion. The institutional review board of Liaoning cancer Hospital & Institute, Shenyang, Liaonin approved this study. Medical archives of the study participants, who had given the authorization for using their medical reports in research, were reviewed. Incident cases in Shenyang, China residents, who were diagnosed with dementia between January 1, 2007 and December 12, 2012 and their respective control subjects were acquired via the medical archival linking system.

Particulars about the medical archival linking and methodology employed to determine cognition impaired cases and control subjects in the cohort were detailed in numerous earlier studies and are shortly described here (Knopman *et al.,* 2011).

Terminology

Using the medical reports and records mapping system all the data for Shenyang, China, people consulted for care in Shenyang are reported by medical diagnoses and methodology. The cognition impaired (dementia) cases were determined using a previously described method (Knopman *et al.,* 2011). Initially, data from medical reports linking system were collected and employed to examine patients having primary cognitive impairment or AD in Shenyang, China, while the study tenure using the diagnosing codes and afterwards remaining data was acquired. The acquired data and the diagnosis were further verified, classified and the year of dementia onset was examined by an experienced neurologist who had wide exposure in handling cognition impaired cases and epidemiological research (Knopman *et al.,* 2003). Diagnostic and Statistical Manual of Mental Disorders (DSM) IV Edition was employed to classify a case having cognitive impairment (Vahia 2013). Each component of the DSM-IV criteria was recorded discretely, and a diagnosis of cognition impairment was made only if every detail of the criteria were fulfilled. Alzheimer was differentiated from other sorts of cognitive impairment based on the accessible clinical and lab reports employing DSM-IV measures (Vahia 2013). Despite the recent modification of measures of AD dementia diagnosis, the basic feature of clinical diagnosis is still reflecting similar features, which are there in the earlier version of DSM-IV.

Subjects who displayed confusion after surgical procedures, and then showed normal consciousness were not considered in this study as demented. Dementia or cognitive abnormalities were demarcated by not including subjects with clear reasons, such as multiple sclerosis, delayed effects of brain injury, anoxic encephalopathy, alcohol use, primary and metastatic glioma and ever enduring psychiatric diseases.

To be considered in our study, patients with cognitive anomalies were required to be inhabitant of Shenyang, China while the year of dementia/cognitive dysfunction was recorded and for tenure of minimum one previous year. Patients with cognitive impairment who relocated to Shenyang, China for the mitigation of previously existing dementia were excluded. Subject's or patient's age at the first appearance of cognitive anomaly was noted based on the data recorded in the medical reports at the time of detection (Knopman *et al.,* 2007).

Selection of controls

For every dementia case/subject, a gender- and age ± 1 year ~ similar control subject was chosen arbitrarily from the normal healthy inhabitants of Shenyang, China who were not having any cognitive abnormality in the reporting (index) year (year of appearance of cognitive impairment in the matched case). The list of all Shenyang, China residents from which the controls were chosen was given by the medical reports archival system (Melton 1996). Control subjects were considered to be devoid of dementia in the case if the examination of particular subject medical records showed no cognitive anomalies or loss of cognitive functions prior to the index-year.

Anaesthesia history data retrieval

In this study, with respective to all patients (cases) and healthy subjects (controls), medical reports were examined and the resultant data were retrieved for every single occurrence of general anesthesia exposure between 45-years of age and the index date. The decision of choosing minimum age limit (>45 years) was based on the experimental experiences and the availability of medical records. The data with respective to the anaesthetic exposures were collected such as agent used for induction, maintenance, the kind of surgical procedure and the duration of exposure. All the retrieved data entry was carried through the Electronic Data Capture system (EDC) (Harris *et al.,* 2009).

STATISTICAL ANALYSES

In this study, the conditional logistic regression (considering the 1:1 matched-case study plan) was employed to determine if the general anaesthetic agents' exposure was accompanying with an augmented possibility of cognitive dysfunction. Most of the patients (incident cases) demonstrated AD dementia. Therefore, we have separately examined all cognitive impairments or the subgroup of AD cases and controls. The analyses in our study, were conducted with anaesthesia encounter measure (1) as any anaesthesia contact (yes or no), (2) as magnitude of encounters (0, 1, 2-3, and 4) and (3) as uninterrupted variables (total duration of encounter in minutes and lengthiest encounter to a single anaesthetic exposure). Analyses were done by SAS, version 9.0, statistical software, USA.

RESULTS

In this study, 601 patients (dementia cases) and 601 gender- and age-matched controls were reported. We have not included 24 matched sets in the final analysis, as 23 cases or controls denied consent for the study and 1 matched age was younger than 45 years, at dementia onset. Finally, the study considered 577 matched cases and control subjects. Each control (devoid of dementia) was followed up for a minimum period of 5-years after index year (the year in which dementia first occurred). Major proportion of cases (n=485; 80.05%) met the diagnosis criteria for AD, with the remaining cases

Table 1: Demographic Characteristic Features[a]

Characteristic feature	Dementia due to all causes[b]		Anomalous cognition owing to Alzheimer disease	
	Controls (N=577)	Cases (N=577)	Controls (N=485)	Cases (N=485)
Age at index date (y), Mean ± SD	79.17±0.7	79.17±0.7	79.17±0.7	79.17±0.7
Gender				
Male n (%)	155 (26.8)	155 (26.8)	138 (28.4)	138 (28.4)
Female n (%)	422 (73.2)	422 (73.2)	347 (71.6)	347 (71.6)
Education (y)				
<12 n (%)	181 (31.3)	190 (32.9)	142 (29.2)	155 (31.9)
12 n (%)	139 (24)	121 (20.9)	98 (20.2)	116 (23.9)
>12 n (%)	236 (40.9)	233 (40.3)	230 (47.4)	198 (40.8)
Unknown n (%)	21 (3.6)	33 (5.7)	15 (3.0)	16 (3.2)

[a]Data are presented as Numbers (Percentage) except where showed otherwise. [b]Cognitive abnormality due to all causes includes any aetiology, with Alzheimer disease.

Table 2: Surgical operation done under the effect of Anaesthesia[a]

Procedure	No. (%) of controls (N=577)	No. (%) of cases (N=577)
Orthopedic	130 (22.5)	128 (22.2)
Obstetrics/gynecology	137 (23.7)	129 (22.4)
General (hernia, appendectomy, etc)	81 (14.0)	83 (14.4)
Breast	41 (7.1)	45 (7.8)
Hepatobiliary	27 (4.7)	31 (5.4)
Urologic	33 (5.7)	31 (5.4)
Oral and maxillofacial	25 (4.3)	27 (4.7)
Vascular	31 (5.4)	29 (5.0)
Major cardiac	18 (3.1)	20 (3.5)
Endocrine	17 (2.9)	15 (2.6)
Ear, nose, and throat	13 (2.3)	14 (2.4)
Ophthalmologic	11 (1.9)	9 (1.6)
Neurosurgery	5 (0.9)	9 (1.6)
Thoracic	3 (0.5)	3 (0.5)
Dermatologic	2 (0.3)	2 (0.3)
Plastic and reconstructive	3 (0.5)	2 (0.5)

[a]Among cases, 414 individuals undergone and 821 operation under the effect of general anesthesia; in the control group, 404 individuals undergone 833 operations. The data showed according to subjects who undergone minimum one-procedure in the given category. Thus, sum across of categories does not equal to the total number of procedures executed.

meeting the dementia criteria (table 1). The median age at the time of the first medical record intake was 32 years (30-46 years) for cases (demented patients) 33 years (23-48) for controls (healthy subjects), and the median interval of the medical record after 45-years and previously to the index year was identical for cases (32.3 years) and controls (33.4 years). Among the 577 cases, 414 (71.7%) were diagnosed who undergone 821 surgical procedures underneath of general anesthesia after 45 years and earlier to the formal detection of dementia. For these 821 surgical procedures tenure of anaesthetic agents' exposure was 90 minutes (35-145 minutes). In the matched control (healthy subjects) group, 404 individuals (70%) underwent 833 surgical procedures with median tenure of anesthesia of 90 minutes (41-139 minutes). Major surgeries included (1256, 76%) the use of a halogenated inhalational anaesthetic drugs.

For major part of surgical procedures, anesthesia induced by sodium thiopental (1505, 91%) and the maintenance anaesthetic agent consisted of nitrous oxide (1485, 89.7%). The types of operations performed were identical in patients with cognitive abnormality and healthy subjects (table 2). In this study, our analysis to examine whether encounters to general anaesthetic agents after 45 years of age was not related with cognitive abnormalities and AD dementia are demonstrated in table 3. When encounters to the general anesthesia was studied as a dichotomous variable (any vs none), anesthesia encounter was not related with cognitive anomalies (OR, 0.87; 95% CI, 0.71-1.09; P=0.29). Additionally, no relation was observed when anaesthetic agents encounter was measured as number of procedures (ORs, 0.83, 0.89, and 1.0 for 1, 2-3 and 4 exposures, correspondingly, compared with no contact as the reference; P=0.52) or when total

cumulative tenure of exposure was examined as an incessant variable (OR, 1.00; 95% CI, 0.89-1.05 per 30-minute increase; P=0.89). Even, when the measures was limited to only cases of AD encounters to general anaesthetic agents (any vs none) was not related with AD cognitive impairment (OR, 0.89; 95% CI, 0.61-1.01; P=0.27).

Furthermore, there was no substantial relationship when anaesthetic agents encounter was measured as total number of operations (ORs, 0.74, 0.79, and 1.15 for 1, 2-3, and 4 exposures, correspondingly; P=0.56) or when total cumulative tenure of exposure was determined as a continuous variable (OR, 1.00; 95% CI, 0.99-1.07 per every 30-minute increase; P=0.77). Examination of risk in association with the each aesthetic agent also has not revealed any relationship with incident dementia.

DISCUSSION

In this study, we observed that exposure of general anesthesia after 45 years age was not linked with dementia occurrence. There have been issues regarding the imminence of cognitive anomalies from anesthesia

Table 3: Relation Between Anesthesia Encounters and Succeeding Dementia[a]

Exposure	Controls	Cases	Odds ratio (OR)	95% CI	P value
Dementia (including Alzheimer dementia) (N=577)					
Any anesthetic	404 (70.0)	414 (71.7)	0.87	0.71-1.09	0.29
Anesthetic exposure					0.52
0	161 (27.9)	158 (27.3)	1.05	Reference	
1	147 (25.4)	139 (24.0)	0.83	0.65-1.17	
2-3	193 (33.4)	198 (34.3)	0.89	0.61-1.12	
≥4	76 (13.1)	82 (14.2)	1.00	0.79-1.31	
Cumulative period of anesthesia (min)[b]	120 (0-294)	115 (0-287)	1.00	0.89-1.05	.89
Cumulative period of anesthesia (min)					0.58
0	155 (26.8)	160 (27.7)	1.03	Reference	
1-120	107 (18.5)	112 (19.4)	0.97	0.67-1.17	
121-240	123 (21.3)	117 (20.2)	0.93	0.79-1.17	
≥241	192 (33.2)	188 (32.5)	0.97	0.76-1.21	
Duration of longest single exposure (min):					0.54
0	162 (28.0)	158 (27.3)	1.01	Reference	
1-120	179 (31.0)	185 (32.0)	0.84	0.57-1.17	
121-240	185 (32.0)	179 (31.0)	0.91	0.75-1.17	
≥241	51 (8.80)	55 (9.5)	1.03	0.71-1.15	
Alzheimer disease (excluding other forms of dementia) (N=485)					
Any anesthetic	421 (86.8)	418 (86.1)	0.89	0.61-1.01	0.27
Anesthetic exposure					0.56
0	64 (13.1)	67 (13.8)	1.01	Reference	
1	164 (33.8)	170 (35.0)	0.74	0.59-1.05	
2-3	177 (36.4)	181 (37.3)	0.79	0.56-1.28	
≥4	80 (16.4)	70 (14.4)	1.15	0.84-1.21	
Cumulative period of anesthesia (min)[b]	160 (0-210)	155 (0-198)	1.00	0.99-1.17	0.77
Cumulative period of anesthesia (min):					0.68
0	64 (13.1)	67 (13.8)	1.00	Reference	
1-120	94 (19.3)	85 (17.5)	0.90	0.67-1.21	
121-240	156 (32.1)	151 (31.1)	0.84	0.63-1.12	
≥241	171 (35.2)	185 (38.1)	0.98	0.79-1.09	
Duration of longest single exposure (min) 0.59					
0	64 (13.1)	67 (13.8)	1.00	Reference	
1-120	162 (33.4)	164 (33.8)	0.78	0.57-1.04	
121-240	191 (39.3)	182 (37.5)	0.88	0.69-1.02	
≥241	68 (14.0)	72 (14.8)	0.97	0.58-1.35	

[a]Data are No. (Percentage) or median. [b]Cumulative period of anesthesia is the total tenure a subject was in contact to general anesthesia agent after 45 years of age and before their index date. The odds ratio (OR) for total anaesthesia tenure shows the increased risk per 30-minutes of anesthesia.

exposure. Memory impairment immediately after surgical procedures under anesthesia is a common phenomenon (Newman *et al.,* 2007). However, a few investigations have exhibited that prolonged cognitive anomaly is also a common finding, which is a serious health concern among general population (Moller JT *et al*., 1998; Vanderweyde *et al*., 2010). There is a considerably greater controversy over the relation between cognitive dysfunctions and anesthesia exposure (Avidan *et al.,* 2011) A recent review suggests that the present evidence is not convincible to ascribe anesthesia exposure for cognitive anomaly after surgical procedures. There are several issues (such as diagnostic criteria etc.,) need to be clarified with respective to the studies which claim the relation between anaesthetic agents encounters and cognitive impairments. While claiming the association of anesthesia with dementia, studies must separate underlying illnesses, surgical stress and ageing; the possibility of previously existing cognitive anomalies and several confounding factors (Ghoneim *et al.,* 2012).

Previously studies have demonstrated that volatile anaesthetic agents can cause caspase stimulation and apoptosis, which results in precipitation of β-amyloid protein (Xie *et al.,* 2007; Bianchi *et al*., 2008; Xie *et al*., 2008; Terrando *et al*., 2010). Even though, a major portion of these clinical studies were done in older rodents, these findings could be seen in younger rodents too (Culley *et al*., 2003; Crosby *et al*., 2005). All these observations provoked a speculation that general anaesthetics could cause acceleration of the biological processes, which may result in AD or its propagation.

The case-control studies would be valuable tools in examining the link between the general anaesthetic encounter and cognitive anomalies (Sprung *et al.,* 2012). A recent systematic review of such case-control studies demonstrated that there is no substantial (pooled odds ratios, 1.05; 95% CI, 0.93-1.19; P=0.43) relation between anesthesia exposure and cognitive anomaly (Seitz *et al.,* 2011). However, this conclusion may not be a robust one, as the studies considered in the meta-analysis suffer from several limitations. The studies have comparatively smaller sample sizes, disparity in selecting controls, lack of information related to anaesthetic exposure and inconsistent diagnostic criteria for AD dementia (Seitz *et al.,* 2011). Major portion of these limitations inclined to bias towards finding no relationship. Yet, other study designs (longitudinal, cross-sectional) also witnessed that there was no relation between general anaesthetic exposure and cognitive anomalies. Our results in this study are according to these previous findings.

Our present study has its own strengths over previous explorations. Our study was based on a geographically limited population, which could reduce probable sampling bias. Recall bias was reduced as there was total admission to reports for a relatively long tenure of diagnosis. Further, stringent diagnosis criteria were considered by expert neurobiologists. Lastly, in this study the sample size is relatively large, which increase the power to detect association.

Findings in this study are in concordance with an earlier study, which reported no association between anaesthesia and cognitive abnormality in patient who underwent coronary artery bypass grafting. Additionally, we found that no relationship between anesthesia and dementia is quite strong in a few sensitivity evaluations (Bednar *et al.,* 2006).

This study has few limitations, for instance the study design (retrospective study) is a limitation. Study subjects enrolment through passive medical record documentation posed a possibility committing errors. Moreover, the control subjects may have comprised of patients with subclinical dementia. In this study, we cannot preclude that any cognitive dysfunction may have altered the decisions to schedule surgeries. The study population, the race and ethnicity of Shenyang, China inhabitants were not unique representatives Peoples Republic China, which could limit the generalizability of present study findings. Lastly, there might be a few other factors that might have an association with the risk of cognitive impairments (Harmanci *et al.,* 2003; Byers *et al.,* 2011). Having witnessed the absence of relation between anaesthetic agents encounter and cognitive abnormalities, it is not likely that the presence of other aspects would substantially alter the deductions.

CONCLUSION

Our study did not show an association between the general anesthesia encounter at >45-years of age and cognitive abnormalities. These findings are an important addition to the existing evidence, which supports the absence of association between anesthesia encounters and dementia risk or cognitive dysfunction.

REFERENCES

Avidan MS and Evers AS (2011). Review of clinical evidence for persistent cognitive decline or incident dementia attributable to surgery or general anesthesia. *J. Alzheimers Dis.,* **24**: 201-216.

Bednar MM, Lee TA, Wolozin B, Weiss KB, Knopman DS and Rocca WA (2006). Coronary artery bypass grafting is not a risk factor for dementia or Alzheimer disease. *Neurology*, **66**: 1785-1785.

Bianchi SL, Tran T, Liu C, Lin S, Li Y, Keller JM, Eckenhoff RG and Eckenhoff MF (2008). Brain and behavior changes in 12-month-old Tg2576 and nontransgenic mice exposed to anesthetics. *Neurobiol. Aging.,* **29**: 1002-1010.

Byers AL and Yaffe K (2011). Depression and risk of developing dementia. *Nat. Rev. Neurol*., **7**: 323-331.

Crosby C, Culley DJ, Baxter MG, Yukhananov R and Crosby G (2005). Spatial memory performance 2 weeks after general anesthesia in adult rats. *Anesth. Analg*., **101**: 1389-1392.

Culley DJ, Baxter M, Yukhananov R and Crosby G (2003). The memory effects of general anesthesia persist for weeks in young and aged rats. *Anesth. Analg.,* **96**: 1004-1009.

Ghoneim MM and Block RI (2012). Clinical, methodological and theoretical issues in the assessment of cognition after anaesthesia and surgery. *Eur. J. Anaesthesiol.,* **29**: 1.

Harmanci H, Emre M, Gurvit H, Bilgic B, Hanagasi H, Gurol E, Sahin H and Tinaz S (2003). Risk factors for Alzheimer disease: A population-based case-control study in Istanbul, Turkey. *Alzheimer. Dis. Assoc. Disord.,* **17**: 139-145.

Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N and Conde JG (2009). Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform*., **42**: 377-381.

Knopman DS, Boeve BF and Petersen RC (2003). Essentials of the Proper Diagnoses of Mild Cognitive Impairment, Dementia, and Major Subtypes of Dementia. *Mayo. Clin. Proc*., **78**: 1290-1308.

Knopman DS, Edland SD, Cha RH, Petersen RC and Rocca WA (2007). Incident dementia in women is preceded by weight loss by at least a decade. *Neurology.,* **69**: 739-746.

Knopman DS, Petersen RC, Rocca WA, Larson EB and Ganguli M (2011). Passive case-finding for Alzheimer's disease and dementia in two U.S. communities. *Alzheimer's Dement.,* **7**: 53-60.

Melton LJ (1996). History of the Rochester Epidemiology Project. *Mayo. Clin. Proc*., **71**: 266-274.

Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE and Gravenstein JS (1998). Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. international study of post-operative cognitive dysfunction. *Lancet* (London, England), **351**: 857-861.

Newman S, Stygall J, Hirani S, Shaefi S and Maze M (2007). Postoperative cognitive dysfunction after noncardiac surgery: A systematic review. *Anesthesiology,* **106**: 572-590.

Seitz DP, Shah PS, Herrmann N, Beyene J and Siddiqui N (2011). Exposure to general anesthesia and risk of Alzheimer's disease: A systematic review and meta-analysis. *BMC. Geriatr.,* **11**: 83.

Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanić K, Welch TL, Olson MD, Hanson AC, Schroeder DR, Wilder RT and Warner DO (2012). Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. *Mayo. Clin. Proc*., **87**: 120-129.

Terrando N, Monaco C, Ma D, Foxwell BMJ, Feldmann M and Maze M (2010). Tumor necrosis factor-triggers a cytokine cascade yielding postoperative cognitive decline. *Proc. Natl. Acad. Sci.,* **107**: 20518-22.

Vahia VN (2013). Diagnostic and statistical manual of mental disorders 5: A quick glance. *Indian J. Psychiatry.,* **55**: 220-223.

Vanderweyde T, Bednar MM, Forman SA and Wolozin B (2010). Iatrogenic Risk Factors for Alzheimer's Disease: Surgery and Anesthesia. *J. Alzheimer's. Dis*., **22**: S91-104.

Xie Z, Culley DJ, Dong Y, Zhang G, Zhang B, Moir RD, Frosch MP, Crosby G and Tanzi RE (2008). The common inhalation anesthetic isoflurane induces caspase activation and increases amyloid β-protein level in vivo. *Ann. Neurol.,* **64**: 618-627.

Xie Z, Dong Y, Maeda U, Moir RD, Xia W, Culley DJ, Crosby G and Tanzi RE (2007). the inhalation anesthetic isoflurane induces a vicious cycle of apoptosis and amyloid-protein accumulation. *J. Neurosci.,* **27**: 1247-1254.