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ORIGINAL ARTICLE

Hippocampal volume reduction in elderly patients at risk for postoperative cognitive dysfunction

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Abstract

Purpose Postoperative cognitive dysfunction (POCD) is a formidable public health issue, which would not only affect the quality of life among elderly patients but also lead to pulmonary infection and increased mortality. While, there is a lack of an effective indicator in predicting POCD. As one pivotal part of the limbic system in brain, hippocampus is associated with cognitive function. Hippocampal atrophy could indicate the degree of changes in cognitive function.

Methods Forty-one ASA II or III patients (23 male, 18 female) aged $\geq$65 years undergoing open gastrointestinal tract surgery were enrolled in this study. MRI was performed to measure the volume of hippocampal formation before surgery and the results were standardized according to individual intracranial volume. All patients underwent a battery of neuropsychological tests including sensitive tests on the Wechsler adult memory scale and Wechsler adult intelligence scale, trail making test and the grooved pegboard test. We used the *Z* score to identify POCD as recommended by ISPOCD. All patients were then divided into POCD group and non-POCD group according to the results of the neuropsychological tests. The results of the tests were correlated with the volume of hippocampal formation measured by MRI. The value of MRI measurement of hippocampal volume in predicting POCD was analyzed. Multivariate linear correlation analyses of compositive *Z* score using potential contributing factors such as age, duration of anesthesia, education and hippocampal volume was carried out.

Results Thirty-six patients completed the whole battery of neuropsychological tests after surgery. Thirteen of the 36 patients were found to have POCD (36 %) on the postoperative 4th day. The hippocampal volume was significantly smaller in POCD group (4.75 $\pm$ 0.23) than in non-POCD group (5.06 $\pm$ 0.31). Hippocampal volume had great influence on *Z* score, and had negative correlation with *Z* score.

Conclusion The MRI measurement of hippocampal volume is suggested to be valuable as a predictor of POCD in the elderly.

Keywords Hippocampus · Cognitive disorders · Postoperative complications · Aged

Introduction

Post-operative cognitive dysfunction (POCD) is the deterioration of cognitive performance following anesthesia and surgery, presenting as impaired memory or concentration, or information processing [1]. POCD is common in older patients following surgery. Its incidence in older patients was as much as 41.4 % at hospital discharge and 12.9 % at 3 months after surgery [2]. Previous studies showed that POCD was independently associated with increased mortality, length of hospital stay, functional disability, placement in long-term care institutions, and hospitalization costs [3]. The profound socioeconomic implications of POCD make it the subject of much investigation [4]. Possible mechanism for POCD included direct toxic effects of anaesthetics, systemic inflammation,

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age-sensitive suppression of neural stem cell function, and acceleration of ongoing endogenous neurodegenerative processes [5]. However, it is still unclear how to predict accurately the occurrence of POCD in older patients.

The hippocampus is an important structure associated with cognitive function. Previous studies showed that reduced hippocampal volume predicted future decline of cognitive performance in cognitively normal older adults at long term follow-up [6–9]. The prediction of hippocampal volume is independent of age and sex in initially healthy elderly participants during a long time. However, whether smaller size of hippocampus is sensitive enough to predict mild cognitive changes of older patients during a short term after anesthesia and surgery or not is still unclear. Therefore, in the present study of older patients we tested hippocampal volume by MRI before surgery, cognitive changes by a battery of neuropsychological tests before and after surgery, and the relationship between hippocampal volume and POCD.

Materials and methods

Patient population

The study was carried out with the approval of the local hospital ethical committee, and informed consent was obtained from each subject. Forty-one ASA II or III patients (23 male, 18 female) aged ≥65 years undergoing open gastrointestinal tract surgery were enrolled in this study. Inclusion criteria for candidates enrolled in this study included: no central nervous system (CNS) lesions, no intake of tranquilizers or antidepressants, no history of cardiovascular or neurological surgery, no family history of mental illness, no history of Alzheimer's disease or Parkinson's disease, no history of alcohol abuse and drug dependence, level of education in line with the completion of neuropsychological tests, score of mini-mental state examination not less than the lowest score of the corresponding education level.

Anesthesia and preoperative management

Patients were premedicated with atropine 0.5 mg and phenobarbital 100 mg, (IM injection, 0.5 h before entering the operating room). Anesthesia in all patients was based on fentanyl (10–20 μg/kg) and midazolam (0.05–0.10 mg/kg), supplemented with isoflurane (1 %) when necessary or with propofol (3–9 mg/kg/h) during surgery. Muscle relaxation was maintained with vecuronium. Standard physiological monitoring—electrocardiogram (ECG), arterial pressure, central venous pressure, arterial oxygen saturation, pressure of end-tidal carbon dioxide ($PETCO_2$), air way pressure, and AAI (auditory evoked potential index). When the blood pressure decreased more than 30 % of the baseline, ephedrine 5–10 mg each time was intravenously injected; when HR < 50 bpm, atropine 0.2 mg each time was intravenously injected; so the BP fluctuations was maintained no more than 30 % of the baseline, HR was maintained within 50–100 bpm, AAI was maintained between 15–25. After surgery patients were sent back to the ward or intensive care unit according to individual status. Patients who developed perioperative hypotension (mean arterial pressure less than 30 % of the patient's usual value) or hypoxemia ($SpO_2 < 90$ %, $PaO_2 < 80$ mmHg)were excluded in this study.

Neuropsychological tests

Neuropsychological tests were performed on the day before surgery and the postoperative fourth day. Test contents included sensitive tests on the Wechsler adult memory scale and Wechsler adult intelligence scale, trail making test and the grooved pegboard test [10, 11]. Test items included: (1) accumulation The subjects were instructed to add the same figure (3 or 4) from 1 to 49, and then the time required to complete and the number of errors and omissions were recorded, roughly segmentation was performed according to the formula; this item may reflect attention and calculation ability; (2) visual reproduction. The subjects were instructed to watch 3 designed graphs a, b, c for 10 s and draw the graphs. Score was estimated depending on the degree of accuracy of the copying graphs [12]; this item may reflect the capacity of visual memory and visual spatial analysis; (3) associative learning. A set of 10 pairs of words was designed for the subject to read in a particular order and the 10 pairs of words, which were written on 10 cards, were presented for the subject to watch at the same time. Then, the tester read the first word and instructed the subject to say another word of its corresponding from memory. After the test had been performed a total of 3 times, score was estimated depending on the degree of accuracy of the answers; this item may reflect the language and visual memory ability; (4) digit span. Both forward and reverse tests were included in which a set of figures was read to the subjects, then the subject repeated the figures forward or reverse and the score was recorded according to the highest order number which was correctly repeated [13]; this item may reflect concentration of attention; (5) digital signs. A set of symbols and figures were arranged, then the subjects matched the figures with symbols. The number of correct answers was regarded as score of this test; this item may reflect psychomotor speed; (6) line. Subjects were instructed to link up figures (including the number of cases) as soon as possible, and the time spent was recorded; this item may reflect attention and psychomotor speed; (7) pegboard. This item was divided into handed and non-handed tests; subjects were instructed to insert the short clubs on specially made boards using handedness and non-handness respectively, and then consuming time was recorded; this item may reflect the velocity of fine movement.

All of these tests were performed in a special room, if the patients were not suitable for moving after surgery, and the tests were implemented at quiet condition.The testers were trained by relevant agencies and didn't know the results of MRI. Tests were performed between 19:00 and 21:00, during which the items of accumulation, visual reproduction, associative learning, digital signs and digit span were carried out randomly using the parallel versions.

To evaluate the false positive rate of the neuropsychological tests in this study, 35 healthy elderly patients (17 male, 18 female, age ≥65 years) in the communities were selected and then tested 2 times at 4 day intervals by the same testing personnel to conduct neuropsychological tests by the same method.

Patients were divided into POCD group and non-POCD group based on whether or not the POCD occurred after surgery, and cognitive function was evaluated by means of the Z score as recommended by ISPOCD [14], concrete steps are as follows:

Each single test was run separately
Standard deviation (s) was calculated based on the first result of single test for healthy elderly
Difference (X_i) of the result of each single test for each patient before and after surgery was calculated
$Z_i = X_i/s$, total Z score $= Z_1 + Z_2 + \cdots + Z_9$
Either Z score of two single test or total Z score ≥1.96 was regarded as the occurrence of the POCD.

Measurement of hippocampal volume

MRI scans of the brain were acquired on all participants using 1.5 T Avanto (Siemens CO., Germany) scanner at The Third Xiangya Hospital. A 3D sequence was acquired from a sagittal localizer in the coronal plane. The following imaging parameters were used: TR = 2400 ms, TE = 3.61 ms, field of view = 24 cm × 24 cm, matrix = 256 × 256, resulting in 160 × 1.2.

On the oblique coronal T1WI [15], hippocampal boundary was outlined from head to tail according to the standard of delimitation of the hippocampus as described in Ref. [13] (Fig. 1). The area of hippocampus for this layer then would be given by computer automatically; the volume for this layer of hippocampus was the result of hippocampal area × thickness, and finally hippocampal volume was obtained by adding the volume for each layer of hippocampus together [16] (Fig. 2). Intracranial volume

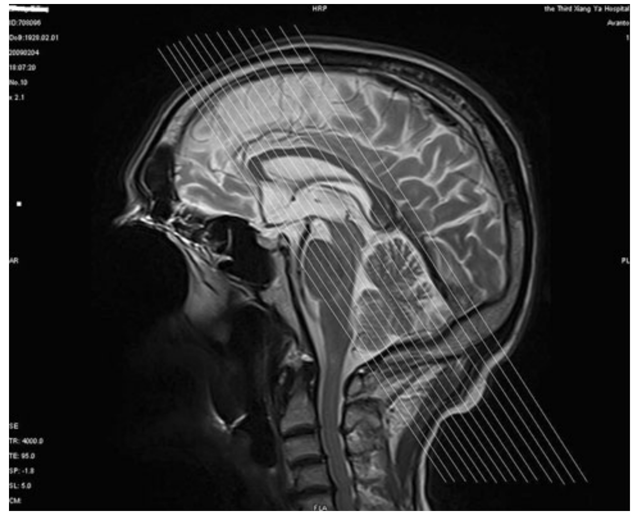

Fig. 1 Oblique coronal T1WI showed the hippocampal volume scanning

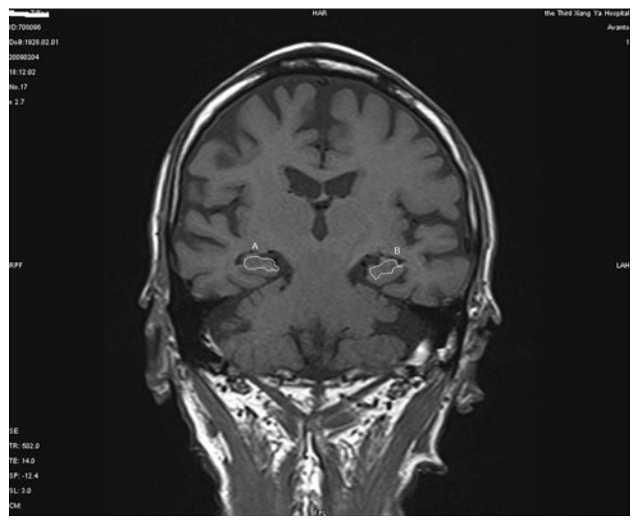

Fig. 2 The *white curve* A and B showed the hippocampal boundary in layer

was measured according to the method by which hippocampal volume was measured, the boundaries of intracranial volume were depicted up layer by layer since the foramen magnum in the T2 weighted cross-sectional image including the brain parenchyma and cerebrospinal fluid but excluding scalp and skull [17], then hippocampal volume was standardized according to intracranial volume, standardized hippocampal volume = (measured hippocampal volume/intracranial volume) × 1000.

Statistical analysis

Statistical analysis was performed using the SPSS 18.0; measurement data were presented as mean ± standard deviation (mean ± SD); group t test or paired t test were

Table 1 Comparison of the indicators of general information between two groups

Index	POCD group ($n = 13$)	Non-POCD group ($n = 23$)
Age (years)	72 ± 8	71 ± 5
Height (cm)	160 ± 7	161 ± 7
Weight (kg)	57 ± 10	52 ± 10
years of education (years)	6 ± 4	7 ± 4
Gender formation (female/male)	5/8	10/13
Intelligence scale score	25.4 ± 1.2	26.4 ± 1.9
ASA (case)		
II	9	16
III	4	7
Duration of operation (min)	182 ± 67	193 ± 92
Duration of anesthesia (min)	218 ± 66	222 ± 103
Dosage of propofol (mg)	297 ± 143	298 ± 131
Dosage of sevoflurane (ml)	16 ± 7	17 ± 6
Utilization rates of vasoactive drugs (%)	54	61

Mean ± SD

applied when comparisons were performed among groups or inner groups respectively, the χ^2 test was applied to determine the significance of differences among count data. Multivariate linear correlation analyses of compositive Z score using potential contributing factors such as age, duration of anesthesia, education and hippocampal volume was carried out. $P < 0.05$ was accepted as statistically significant.

Results

One patient did not have preoperative MRI scan of the head; 2 patients could not complete neuropsychological tests due to disease progression after surgery and 2 patients refused postoperative neuropsychological tests, so a total of 36 patients completed the whole battery of neuropsychological tests, among whom 13 patients (incidence was 36 %) were found to have POCD. All of the 35 healthy elderly patients finished the neuropsychological tests two times, among whom 2 met the diagnostic criteria of POCD, so the false positive rate of the neuropsychological tests which were applied to diagnose POCD in this study was 5.7 %.

The indicators of general characteristic and the indicators of intraoperative conditions were no significant difference ($P \geq 0.05$) (Table 1).

The postoperative results of neuropsychological tests including accumulation, visual reproduction, associative learning, digit span-backward fell down in POCD group compared with preoperative ones, while in non-POCD group, cumulative results of neuropsychological tests fell down too ($P < 0.05$). Total composite Z score of POCD group was higher than that of non-POCD group ($P < 0.01$) (Table 2).

The hippocampal volume of POCD group (4.75 ± 0.23) was smaller than that of the non-POCD group (5.06 ± 0.31) ($P < 0.01$) (Table 3). After an enter model of multivariate linear correlation analyses, only hippocampal volume had great influence on Z score, and had negative correlation with Z score ($B = -1.940$, $\beta = -0.346$, $P = 0.044$), while other indicators had very little effect on Z score (Table 4).

Discussion

The indicators of general information and the indicators of intraoperative conditions had no significant difference, which was among groups. In this study AAI was maintained between 15 and 25 and the vital signs of patients during surgery had no significant fluctuations, which excluded the impacts of both anesthesia depth and intense fluctuations of hemodynamics imposed on the results of tests.

The present study applied neuropsychological tests to estimate POCD yielding a high specificity and sensitivity. The visual verbal learning test, conversion of concept into task test and alphanumeric symbol test in the neuropsychological tests (including 6 items) as recommended by ISPOCD were basically similar to associative learning, line, digital signs respectively which were used in present study. The neuropsychological tests applied in this study could objectively reflect the cognitive function of human beings.

In this study, a parallel version was adopted to reduce the learning effect during testing; each test was carried out by the same personnel in the same environment at the same time in order to overcome the variability. As reported by Lewis, the sensitivity of test methods can be improved by increasing neuropsychological testing programs; however, the cost is significantly increased at a false positive rate. Since a false positive rate can affect the results of POCD related research, similar results of these are not comparable [18]. The false positive rate of neuropsychological tests which were applied to diagnose POCD in this study was 5.7 %, which was similar to the false positive rate of neuropsychological tests recommended by ISPOCD (3.4 %), so the results of neuropsychological tests presented high reliability.

For soft tissue, MRI has good contrast resolution and the characteristics of multi-directional imaging, so true anatomical cross-section images of brain structure from each

Table 2 Comparison of neuropsychological tests results and Z scores between two groups

	Time	POCD group ($n = 13$)	Non-POCD group ($n = 26$)
Accumulation (point)	Preoperative	55.93 ± 25.3	71.59 ± 21.0
	Postoperative	28.54 ± 42.66*	62.78 ± 18.31△
Visual reproduction (point)	Preoperative	10.12 ± 1.88	9.95 ± 2.02
	Postoperative	8.04 ± 2.70△	9.21 ± 1.92
Associative learning (point)	Preoperative	13.50 ± 2.17	13.13 ± 4.23
	Postoperative	9.92 ± 2.64△	12.28 ± 3.50
Digit span-forward (point)	Preoperative	5.59 ± 1.55	5.82 ± 0.94
	Postoperative	5.84 ± 1.62	5.78 ± 1.38
Digit span-reverse (point)	Preoperative	3.23 ± 1.16	2.78 ± 0.60
	Postoperative	2.69 ± 1.65△	2.65 ± 0.49
Digital signs (point)	Preoperative	17.84 ± 9.40	17.40 ± 4.29
	Postoperative	16.23 ± 5.64	15.78 ± 4.55
Line (second)	Preoperative	62.53 ± 13.38	64.21 ± 15.26
	Postoperative	63.92 ± 11.03	64.17 ± 14.01
Pegboard-handed (point)	Preoperative	63.77 ± 10.95	62.52 ± 11.18
	Postoperative	64.54 ± 10.95	64.39 ± 10.89
Pegboard-non-handed (point)	Preoperative	74.00 ± 16.11	72.60 ± 10.64
	Postoperative	75.92 ± 10.78	75.57 ± 14.44
Z score		3.72 ± 0.71	0.82 ± 1.05#

Shown as (mean ± SD)

Comparison of preoperative and postoperative results within each group, for *$P < 0.05$, for △$P < 0.01$

Comparison between POCD group and non-POCD group, for #$P < 0.01$

Table 3 Comparison of hippocampal volume between two groups

	All patients ($n = 36$)	POCD group ($n = 13$)	Non-POCD group ($n = 26$)
Left hippocampal	2.38 ± 0.19	2.26 ± 0.21	2.45 ± 0.15△
Right hippocampal	2.57 ± 0.18#	2.49 ± 0.11&	2.62 ± 0.20*,#
Total	4.95 ± 0.32	4.75 ± 0.23	5.06 ± 0.31△

Shown as (mean ± SD)

Comparison between POCD group and non-POCD group, for *$P < 0.05$, for △$P < 0.01$

Comparison of left and right hippocampal volume within each group, for &$P < 0.05$, for #$P < 0.01$

Table 4 Multivariate linear correlation to determine factors associated with composite Z score

Variables	B values	SE	β	t values	P values
Hippocampal volume	−1.940	0.925	−0.346	−2.097	0.044
Years of education	−0.001	0.071	−0.003	−0.019	0.985
Age	0.026	0.052	0.090	0.507	0.616
Duration of anesthesia	0.001	0.004	0.045	0.261	0.796

$R^2 = 0.126$

layer can be shown clearly. Because of the complex structure of hippocampal volume, MRI scan performed on the oblique coronal is a preferable method of imaging observation at present. Since hippocampal volume can be affected by intracranial volume leading to the lack of comparability of data. The present study standardizes hippocampal volume with intracranial volume to eliminate the impacts of intracranial volume imposed on hippocampal volume.

The hippocampus is a structure often implicated in normal learning and memory and process of hippocampal volume atrophy reflects the decreased cognitive function. Seab [19] first discovered that the hippocampal volumes of patients with AD shrank 40 % compared with healthy elderly. Frisoni evaluated the atrophies of hippocampus and entorhinal cortex among patients with AD, frontotemporal dementia patients, and healthy elderly. The results revealed that the atrophies of both hippocampus and entorhinal cortex in frontotemporal dementia patients were more severe than that in healthy subjects; moreover, the atrophies could discriminate AD from healthy controls, yielding a sensitivity of 80 % and an accuracy of 85 % [20]. In a three-year investigation that preformed in 58 healthy elderly with a mean age of 81, Jack [21] found that the rates of hippocampal atrophy were markedly different when the changes of cognitive function were different; the elderly whose cognitive function declined to MCI or AD showed a rate of atrophy by 2.8 ± 1.7 % annually.

Currently, the lack of consensus on the accurate boundary of hippocampus and standardized protocol for analysis leads to poor reproducibility. However, most studies implicated that the degree of hippocampal atrophy was an indicator of brain degenerative changes; the degree of hippocampal atrophy was associated with cognitive function [22], which is in agreement with the results of the present study. We show that the hippocampal volume of POCD group is smaller than that of non-POCD group, hippocampal volume has a negative correlation with Z score; hippocampal volume is an independent risk to predict POCD. We also found that age, the level of education and anesthesia duration were not independent risk factors in the pathogenesis of POCD, which is different from others [3–5]. It is presumed that these discrepancies might derive from the relatively small sample size, similar curative operation, as well as marginal differences in the age of participants, the levels of education and anesthesia duration. Indicates that the MRI measurement of hippocampal volume is valuable as a predictor of POCD in elderly patients.

It is a possible limitation of the present study that we did not assess functional hippocampal changes in predicting the POCD. The microstructural abnormalities as revealed by diffusion tensor imaging (DTI) are very sensitive early indicators of hippocampal dysfunction [23]. To a certain extent, the neuropsychological assessment could be influenced by emotion and pain; even though we performed postoperative analgesia for each patient, a scale is still required to objectively evaluate the degree of pain and emotional changes of patients. In addition, we neglect the impacts of postoperative complications on cognitive function. These issues will be taken into account in our subsequent studies.

In conclusion, structural magnetic resonance imaging (MRI) scans have been used primarily to predict POCD, and we found that the hippocampal volume measured preoperatively was significantly smaller in POCD group than in non-POCD group. A further study with the larger sample size is needed to confirm the value of the measurement of hippocampal volume as a predictor of POCD.

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Conflict of interest None.

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