Cognitive Impairment in Aneurysmal Subarachnoid Hemorrhage Patients with Delayed Cerebral Infarction: Prevalence and Pattern

Alberto Chi Ho Chu, George Kwok Chu Wong, Sandy Wai Lam, Adrian Wong, Karine Ngai, Wai Sang Poon, and Vincent Mok

Abstract *Background*: Cognitive deficits commonly occur after aneurysmal subarachnoid hemorrhage (aSAH) and clinical understanding is important for treatment and rehabilitation. Delayed cerebral infarction was shown to be related to poor outcome. Data on delayed cerebral infarction-related cognitive impairment were lacking.

Objective: We investigated the prevalence and pattern of delayed cerebral infarction-associated cognitive impairment.

Methods: We carried out a prospective observational and diagnostic accuracy study in Hong Kong in patients aged 21–75 years with aSAH who had been admitted within 96 h of ictus. The domain-specific neuropsychological assessment battery at 1 year after ictus was used for cognitive assessments. A cognitive domain deficit was defined as a cognitive domain z score less than −1.65 (below the fifth percentile). Cognitive impairment was defined by two or more cognitive domain deficits. The current study is registered at ClinicalTrials.gov of the U.S. National Institutes of Health (NCT01038193).

Results: One hundred and twenty aSAH patients were recruited. Patients with delayed cerebral infarction (DCI) have cognitive impairment more frequently (22 % vs 11 %; odds ratio: 2.2, 0.6 to 7.8, $p=0.192$). Cognitive domain deficits commonly affected in aSAH patients with delayed cerebral infarction were verbal memory, language, and visuospatial memory and skill domains, and were relatively uncommon in aSAH patients without delayed cerebral infarction.

Conclusion: In patients with aSAH, delayed cerebral infarction was associated with a specific pattern of cognitive domain deficits. The pathophysiology should be further investigated.

Keywords Aneurysm • Cognitive impairment • Stroke Subarachnoid hemorrhage

A.C.H. Chu, MRCS • G.K.C. Wong, MD (✉) • S.W. Lam, BSocSc
K. Ngai, BSocSc • W.S. Poon, FRCS
Division of Neurosurgery, Department of Surgery,
Prince of Wales Hospital, The Chinese University of Hong Kong,
4/F Clinical Science Building, 30-32 Ngan Shing Street,
Shatin, NT, Hong Kong SAR, China
e-mail: georgewong@surgery.cuhk.edu.hk

A. Wong, PhD
Department of Psychological Studies,
The Hong Kong Institute of Education, 10 Lo Ping Road,
Tai Po, NT, Hong Kong

V. Mok, MD
Division of Neurology, Department of Medicine and Therapeutics,
Prince of Wales Hospital, The Chinese University of Hong Kong,
4/F Clinical Science Building, 30-32 Ngan Shing Street,
Shatin, NT, Hong Kong SAR, China

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) accounts for 3 % of strokes. Estimated independence after aSAH varied between 36 and 60 % only [1, 10]. Global and focal neurological deficit in aSAH survivors has been well documented. Recent studies showed that cognitive impairment in aSAH patients might affect their functional outcomes and 27–44 % of patients who returned to the community exhibited cognitive dysfunction [11, 14, 15]. Thus, it is clinically important to better understand the pattern of cognitive dysfunction after aSAH.

The exact cause of cognitive impairment after SAH is not clear. It is postulated that the primary and secondary brain injury, such as delayed cerebral infarction, may contribute to the functional deficit of the patients. Reports in the literature have confirmed that delayed cerebral infarction is related to poor outcome [16, 17, 20]. However, data on the prevalence or pattern of delayed cerebral infarction-related cognitive impairment are lacking. With this in mind, we designed the current study.

J. Fandino et al. (eds.), *Neurovascular Events After Subarachnoid Hemorrhage*, Acta Neurochirurgica Supplement, Vol. 120,
DOI 10.1007/978-3-319-04981-6_51, © Springer International Publishing Switzerland 2015

Methods

This prospective observational study was performed in four neurosurgical centers in Hong Kong [16–18]. It is registered at ClinicalTrials.gov of the US National Institutes of Health (NCT01038193) and was approved by hospital ethics committees. This study conforms to the Declaration of Helsinki, and written informed consent was obtained from all of the participants or their next of kin.

The patient inclusion criteria were: (1) spontaneous SAH with angiography-confirmed etiology of intracranial aneurysm; (2) hospital admission within 96 h after ictus; (3) age between 21 and 75 years of age; (4) a speaker of Chinese (Cantonese); and (5) informed consent from the patients or their next of kin. The patient exclusion criteria were: (a) a history of previous cerebrovascular or neurological disease other than unruptured intracranial aneurysm or (b) a history of neurosurgical operation before ictus.

Assessments [17, 18]

Assessments were conducted 3 years after ictus by one of the two research assistants (psychology graduates) trained and supervised by a postdoctoral research psychologist. The battery of cognitive assessments had previously been reported in our local Chinese population [17–19]. The choice of the battery of cognitive assessments was based on: (a) previous cognitive studies in local Chinese patients and standard cognitive tests validated in the Cantonese-speaking population; and (b) a balanced battery covering verbal and visuospatial memory, attention and working memory, executive functions, psychomotor speed, and language.

A. Verbal memory domain
   1. Hong Kong List Learning Test (HKLLT) [3]. The HKLLT was developed based on the California Verbal Learning Test, which has been used in vascular cognitive impairment studies. It is a verbal learning and memory test that consists of two 16-word lists with three learning trials with immediate recall, 10-min delayed recall, and 30-min delayed recall and recognition for each list. The HKLLT has been validated in both healthy and pathological local populations.

B. Visuospatial skill and memory domain
   1. The Rey Osterrieth Complex Figure is a commonly used test for assessing visuospatial construction skills and visuospatial memory [5, 9].

C. Attention and working memory domain
   1. Verbal and visual digit span forward and backward from the Chinese Wechsler Memory Scale Third Edition for the examination of simple attention and working memory [6, 13]. Verbal and visual spans have been used as donor scales for composite psychometric measures.

D. Executive function and psychomotor speed domain
   1. Symbol–Digit Modalities Test. This brief, easy-to-administer, timed coding test is a variant of the Digit–Symbol Coding Task in the Wechsler Adult Intelligence Scale—Third edition. Timed coding tasks have been used in studies that involve subjects with suspected vascular cognitive impairment.
   2. Color Trails Test (CTT). This test originated from the Trail Making Test (TMT), which is used for the timed assessment of psychomotor speed and executive functions. Using colored numbers instead of the English alphabet, the CTT is considered to be an acceptable cultural substitute for the original TMT with similar psychometric properties [7].
   3. Animal Fluency. This test requires subjects to generate as many animal names as possible in 1 min. It is a simple timed test that sensitively measures speed and activation, as well as such executive processes as clustering, set shifting, and retrieval [4, 8].

E. Language domain
   1. Modified Boston Naming Test (mBNT). The Boston Naming Test is the most frequently used confrontation naming test for assessing language. Here, we have used a validated modified version that contains 15 stimuli appropriate for use in Chinese cultures.

Cognitive domain scores were computed by averaging the z scores of the respective test measures derived from the established age-matched and education-matched norms. A cognitive domain deficit was defined through a cognitive domain z score less than −1.65 (below the fifth percentile). We used the presence of two or more cognitive domain deficits rather than any cognitive domain deficits as the definition of cognitive impairment as in neuropsychological outcome study of the International Subarachnoid Aneurysm Trial (ISAT) [12].

Statistical Analysis

The statistical analyses were generated using IBM SPSS Statistics for Windows 21 (SPSS, Chicago, Illinois, USA). Categorical data are presented as number (percentages) and numerical data are presented as means ± standard deviations (SD), unless otherwise stated. Categorical data were analyzed using the chi-square test or Fisher's exact test, and continuous data were analyzed using the unpaired Student's t-test or Mann–Whitney U-test, as appropriate. Statistical significance was indicated by a two-tailed probability value of less than 0.05

Results

One hundred and twenty patients completed the neurocognitive assessment at 1 year. The patient cohort was previously reported [17]. In brief, the patient characteristics are shown in Table 1. One hundred and five (88 %) patients had favorable outcome as defined by the modified Rankin Scale (mRS) 0–2.

One or more cognitive domain deficits were found in 6 (32 %) patients with delayed cerebral infarction and 23 (23 %) patients without delayed cerebral infarction (odds ratio: 1.57, 0.54–4.58, $p=0.290$). Cognitive impairment (two or more domain deficits) was found in 4(21 %) patients with delayed cerebral infarction and 11(11 %) patients without delayed cerebral infarction (odds ratio: 2.18, 0.61–7.76, $p=0.192$).

Table 1 Patient profiles

	Patients assessed ($n=120$)
Age, median (IQR)	51 years (46–61 years)
Women	82 patients (68 %)
Hypertension	41 patients (34 %)
Smoker	31 patients (26 %)
WFNS grade	
I	73 patients (61 %)
II	29 patients (24 %)
III	3 patients (2 %)
IV	11 patients (9 %)
V	4 patients (3 %)
Location of aneurysm	
Anterior cerebral artery	31 patients (26 %)
PComA	18 patients (15 %)
ICA other than PComA	23 patients (26 %)
Middle cerebral artery	31 patients (26 %)
Posterior circulation	16 patients (13 %)
Aneurysm treatment	
Coiling	59 patients (49 %)
Clipping	56 patients (47 %)
Delayed cerebral infarction	19 patients (16 %)
mRS	
0	36 patients (30 %)
1	21 patients (18 %)
2	48 patients (40 %)
3	13 patients (11 %)
4	1 patients (1 %)
5	1 patients (1 %)

IQR interquartile ranges, *PComA* posterior communicating artery, *ICA* internal carotid artery, *WFNS* World Federation of Neurosurgical Societies, *mRS* modified Rankin Scale

Cognitive domain deficits commonly affected in aSAH patients with delayed cerebral infarction were verbal memory (21 % vs 4 %; odds ratio: 6.47, 1.45–28.66, $p=0.021$), language (16 % vs 6 %; odds ratio: 2.97, 0.67–13.09, $p=0.152$), and visuospatial memory and skill (13 % vs 5 %; odds ratio: 2.42, 0.75–7.83, $p=0.126$) domains (Table 2).

Discussion

Functional outcome of patients with aSAH is usually assessed by mRS. Cognitive domain function can interact with the patient's physical ability in determining his or her real functional independence. This interaction also affects the potential and capability of patients in returning to their usual work and usual quality of life.

We showed that DCI worsened cognitive domain functions in aSAH patients and that verbal memory domain deficit was significantly associated with DCI. Verbal memory is predominantly mediated by the medial temporal lobes, including the hippocampus and parahippocampus network. A previous study showed significant reduction in bilateral hippocampal volumes among patients with aSAH [2]. A similar finding was observed in visuospatial memory and function domain and language domain.

The proportions of patients with executive and psychomotor speed domain deficit are similar in those with and without DCI. The executive function is predominantly mediated by the frontal lobes and it encompasses higher cortical function such as planning, inhibition, problem solving, attention, and decision making [1]. One possibility that two groups of patients have a similar prevalence of executive function domain deficit is that the executive and psychomotor speed domain function may be mainly affected by the primary hemorrhage.

There were limitations in the current study. First, although the domain-based neuropsychological battery we used has been validated in a Chinese population with established norm, it is possible that it was not sensitive enough to measure subtle cognitive changes. Second, the cognitive domain outcomes are dichotomized for analyses and the patient number did not allow matched analyses. Finally, fatigue can adversely affected performance because the battery of cognitive assessments is tiring.

Conclusion

In conclusion, our study showed a distinct pattern of cognitive domain deficits in a prospective observational SAH cohort. These findings should be further investigated in future multicenter prospective studies.

Table 2 Cognitive domain deficit in patients with and without delayed cerebral infarction (DCI)

	Patients with DCI (%) ($n=19$)	Patients with no DCI (%) ($n=101$)	Odds ratio (95 % CI)	p-value
Verbal memory domain deficit	4 (21)	4 (4)	6.47 (1.45–28.66)	0.021*
Visuospatial skill and memory domain deficit	5 (26)	13 (13)	2.42 (0.75–7.83)	0.126
Attention and working memory domain deficit	2 (10)	6 (6)	1.86 (0.35–10.01)	0.371
Language domain deficit	3 (16)	6 (6)	2.97 (0.67–13.09)	0.152
Executive function and psychomotor speed domain deficit	2 (11)	10 (10)	1.07 (0.22–5.32)	0.600
Cognitive impairment	4 (21)	11 (11)	2.18 (0.61–7.76)	0.192

DCI delayed cerebral infarction
*$p<0.05$

Conflict of Interest Statement/Financial Disclosure We declare that we have no conflict of interest.

References

1. Al-Khindi T, Macdonald RL, Schweizer TA (2010) Cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. Stroke 41:e519–e536
2. Bendel P, Koivisto T, Hänninen T, Kolehmainen BM, Könönen M, Hurskainen H, Pennanen C, Vanninen R (2006) Subarachnoid hemorrhage is followed by temporomesial volume loss. Neurology 67:575–582
3. Chan AS, Kwok I (1999) Hong Kong list learning test: manual and preliminary norm. Department of Psychological and Clinical Psychology Center, Hong Kong
4. Dikmen S, Corrigan JD, Levin HS, Machamer J, Stiers W, Weisskopf MG (2009) Cognitive outcome following traumatic brain injury. J Head Trauma Rehabil 24:430–438
5. Lam CL, Gandek B, Ren XS, Chan MS (1998) Tests of scaling assumptions and construct validity of the Chinese (HK) version of the SF-36 health survey. J Clin Epidemiol 51:1139–1147
6. Lam CL, Lauder IJ, Lam TP, Gandek B (1999) Population based norming of the Chinese (HK) version of the SF-36 health survey. H K Pract 21:460–470
7. Lee TM, Chan CC (2000) Are trail making and color trails tests of equivalent constructs? J Clin Exp Neuropsychol 22:529–534
8. Lim PP, Ng LL, Chiam PC, Ong PS, Ngui FT, Sahadevan S (2000) Validation and comparison of three brief depression scales in an elderly Chinese population. Int J Geriat Psychiatry 15:824–830
9. Rey A (1941) L'examen psychologique dans les cas d'encephalopathie traumatique. Arch de Psychologie 28:296–302
10. Rinkel GJ, Algra A (2011) Long-term outcomes of patients with aneurysmal subarachnoid haemorrhage. Lancet Neurol 10:349–356
11. Schweizer TA, Al-Khindi T, Macdonald RL (2012) Mini-mental state examination versus Montreal cognitive assessment: rapid assessment tools for cognitive and functional outcome after aneurysmal subarachnoid hemorrhage. J Neurol Sci 316:137–140
12. Scott RB, Eccles F, Molyneux AJ, Kerr RS, Rothwell PM, Carpenter K (2010) Improved cognitive outcomes with endovascular coiling of ruptured intracranial aneurysms: neuropsychological outcomes from the International Subarachnoid Aneurysm Trial. Stroke 41:1743–1747
13. Wechsler D (2005) Wechsler Memory Scale III (Chinese): manual. Psychological Corporation, Taiwan
14. Wong GK, Wong R, Mok VC, Fan DS, Leung G, Wong A, Chan AS, Zhu CX, Poon WS (2009) Clinical study on cognitive dysfunction after spontaneous subarachnoid haemorrhage: patient profiles and relationship to cholinergic dysfunction. Acta Neurochir 151:1601–1607
15. Wong GK, Wong R, Mok VC, Wong A, Poon WS (2010) Natural history and medical treatment of cognitive dysfunction after spontaneous subarachnoid haemorrhage: review of current literature with respect to aneurysm treatment. J Neurol Sci 299:5–8
16. Wong GK, Lam SW, Ngai K, Wong A, Mok V, Poon WS, Cognitive Dysfunction after Aneurysmal Subarachnoid Haemorrhage Investigators (2012) Evaluation of cognitive impairment by the Montreal cognitive assessment in patients with aneurysmal subarachnoid haemorrhage: prevalence, risk factors and correlations with 3 month outcomes. J Neurol Neurosurg Psychiatry 83: 1112–1117
17. Wong GK, Lam SW, Ngai K, Wong A, Poon WS, Mok V, Cognitive Dysfunction after Aneurysmal Subarachnoid Haemorrhage Investigators (2013) Cognitive domain deficits in patients with aneurysmal subarachnoid haemorrhage at 1 year. J Neurol Neurosurg Psychiatry 84:1054–1058
18. Wong GK, Lam SW, Wong A, Ngai K, Poon WS, Mok V (2013) Comparisons of Montreal Cognitive Assessment and Mini-Mental State Examination in evaluating cognitive domain deficit following aneurysmal subarachnoid haemorrhage. PLoS One 8(4):e59946
19. Wong GK, Ngai K, Wong A, Lam SW, Mok VC, Yeung J, Rainer T, Wong R, Poon WS (2011) Long-term cognitive dysfunction in patients with traumatic subarachnoid hemorrhage: prevalence and risk factors. Acta Neurochir 154:105–111
20. Wong GK, Poon WS (2013) Clinical, transcranial Doppler ultrasound, radiological features and prognostic significance. Acta Neurochir Suppl 113:9–11