Correlation of Common Carotid Artery Intima Media Thickness, Intracranial Arterial Stenosis and Post-stroke Cognitive Impairment

Yong-Hui Lee and Shoou-Jeng Yeh

Abstract-

Background and Purpose: Atherosclerosis of the intracranial arteries is a well-recognized cause of ischemic stroke in Asians, and extracranial carotid artery disease is more often seen in western countries. The relationship of common carotid artery intima-media thickness (CCA-IMT), intracranial arteries stenosis (ICS) and vascular cognitive impairment (VCI) after ischemic stroke has not been fully elucidated. In this study, we investigated the relationship between CCA-IMT and the severity of ICS and VCI.

Methods: We recruited patients from December 2004, to June 2005, with the inclusion criteria: (1) first-ever ischemic stroke, (2) admission within 3 days of stroke onset, (3) under 80 years old, and (4) no previous dementia history. We excluded patients with stroke scores greater than an NIHSS of 15; those with recurrent stroke, and those with extracranial internal carotid artery stenosis >50%. All the patients underwent brain MR angiography, carotid ultrasonography and neuropsychological testing during hospitalization and at 3 months after stroke. We defined the percent of ICS using the method of Warfarin-Aspirin Symptomatic Intracranial Disease. Measurement of CCA-IMT was made on the far wall of the common carotid artery, 1.5 cm proximal to the bifurcation at a point free of plaques. Cognitive performance was assessed using the Cognition Assessment State Instrument (CASI).

Results: Thirty patients (21M/9F, mean age 65.97±10.33 years) were studied. The initial CCA-IMT was 1.04±0.59 mm and the initial CASI was 64.73±14.75. The ICS was 70±26%. At 3 months after stroke, the CCA-IMT was 1.06±0.59 mm; and CASI was 70.07±18.50. Compared with patients with CCA-IMT > 0.87 mm, those with CCA-IMT ≤ 0.87 mm had lower ICS (57±23% vs. 81±24%, $p=0.013$), but similar initial CASI score (67.92±13.52 vs. 61.93±16.64, $p=0.28$). The improvement of CASI score at 3 months was significantly higher in patients with CCA-IMT ≤ 0.87 mm (67.92±13.52 vs. 77.36±14.12, $p=0.001$), than those with CCA-IMT > 0.87 mm (61.93±16.64 vs. 63.69±19.89, $p=0.612$).

Conclusions: CCA-IMT might be associated with the severity of ICS and VCI at 3 months after the first-ever ischemic stroke. The patients with lower CCA-IMT had a better CASI evaluation at 3 months after stroke. A larger scale of study to explore the association of CCA-IMT, VCI and ICS at 3 months after stroke might help farther delineation of these relationships.

Key Words: Common carotid artery intima-media thickness, Intracranial arterial stenosis, Vascular cognitive impairment, Acute ischemic stroke

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INTRODUCTION

Atherosclerotic stenosis of the major intracranial arteries is a well recognized cause of ischemic stroke in Asians, whereas extracranial carotid artery disease is more common in western countries[1-5]. Recently, common carotid artery intima-media thickness (CCA-IMT) has been identified as a vascular risk factor. Increased CCA-IMT values have been associated with an atherosclerotic process in the intracranial arteries and with stroke[6,7]. Vascular cognitive impairment (VCI) after a stroke may develop into 'vascular dementia'[8]. The relationship of CCA-IMT, intracranial arterial stenosis (ICS) and VCI after ischemic stroke has not been fully elucidated. We therefore investigated the association of CCA-IMT, ICS and VCI in patients at admission and three months after a first-ever ischemic stroke.

METHODS

Subject

We prospectively recruited from December 2004, to June 2005, using the following inclusion criteria: (1) first-ever ischemic stroke, (2) admission within three days of the stroke symptoms onset, (3) patients under 80 years of age, and (4) patients with no dementia history. We excluded the patients with (1) stroke severity greater than NIHSS of 15), (2) recurrent stroke, and (3) extracranial internal carotid artery (ICA) stenosis >50%. All patients underwent brain magnetic resonance angiography (1.5 Telsa TOF MRA without contrast), carotid ultrasonography and neuropsychological test during admission, and the CCA-IMT and neuropsychological test were repeated at three months after stroke. This study was approved by the hospital's IRB (Institutional Review Board) and all participating patients had provide informed consent before entering the study.

Carotid ultrasonography

All patients underwent carotid ultrasonography during hospitalization and at 3 months post-stroke by one experienced technician using an Agilent SONOS 4500, with a 7.5-MHz linear array transducer manufactured in Andover, Massachusetts. Measurement of intima-media thickness was made on longitudinal B mode images of the far wall of the common carotid artery (CCA), 1.5 cm proximal to the bifurcation, at a point free of plaques. According to Talelli et al. reports of post-stroke cognitive impairment[9], we arbitrarily categorized patients into two groups with CCA-IMT ≤ 0.87 mm and CCA-IMT > 0.87 mm to investigate their correlation to the variables.

Assessment of cognition

All patients were administered the Cognition Assessment State Instrument (CASI)[10] during hospitalization and at the third month post-stroke by a single investigator. CASI, scores below 80/100 (educated) and 50/100 (uneducated) are considered to be indicative of cognitive impairment.

Measuring intracranial arterial stenosis

We selected the diseased vessels by measuring the middle cerebral arteries (MCA) and intracranial ICA as the ICS because the intracranial ICA and MCA are the continuation of the CCA, and the cognitive function is more vulnerable with an MCA territory lesion. We defined the percentage of stenosis of an intracranial artery using the WASID method[11-13], the equation was as follows: percent stenosis = $[(1-(D_{stenosis}/D_{normal}))] \times 100$ (Fig.), where $D_{stenosis}$ = the diameter of the artery at the site of the most severe degree of stenosis and D_{normal} = the diameter of the proximal normal artery. D_{normal} was determined by the following criteria: For the MCA, anterior cerebral artery (ACA), posterior cerebral artery (PCA), intracranial vertebral artery (VA) and basilar artery (BA), the diameter of the proximal part of the artery at its widest, non-tortuous, normal segment was chosen (first choice). If the proximal artery was diseased (i.e., MCA origin stenosis), the diameter of the distal portion of the artery at its widest, parallel, non-tortuous normal segment was substituted (second choice). If the entire intracranial artery was diseased, the most distal, parallel, non-tortuous normal segment of the feeding artery was measured (third choice) (i.e., measured at dominant VA if the entire BA was diseased, measured at supraclinoid carotid artery if the entire MCA was dis-

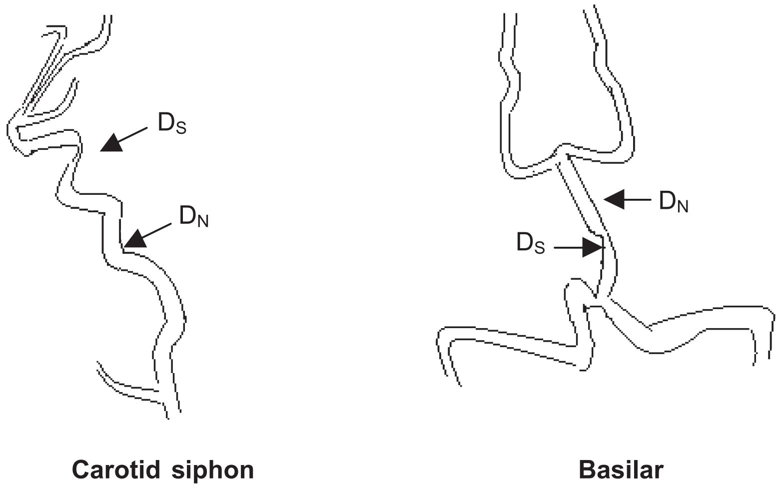


Figure. WASID Method: Warfarin-Aspirin Symptomatic Intracranial Disease. Ds: Diameter of stenotic lumen; Dn: Diameter of normal lumen.

eased). If tandem intracranial lesions were present, the most severe stenosis was selected. For a 'gap sign' (i.e., the lumen of the vessel could not be visualized at the site of severe stenosis), the percent stenosis was defined as 99%.

All the measurements of the intracranial arteries were made on the image monitor using computerized scale marked in 0.1-mm increments. Inter-observer agreement in the difference of percent stenosis measured by two readers was less than 10%.

Statistical analysis

Between-group comparisons were made with the t-test for continuous variables and Chi-square test for categorical data. Tests were two-tailed and the results were considered significant at P<0.05. Univariate correlates were assessed using Pearson correlation. Analyses were conducted using SPSS version 9.0 for windows (SPSS Inc.).

RESULTS

Thirty patients were recruited in this study (21 males and 9 females) with a mean age of 65.97±10.33 years. The initial CCA-IMT was 1.04±0.59 mm. The initial CASI was 64.73±14.75. The ICS was 70±26%. At three months after stroke, the CCA-IMT was 1.06±0.59 mm; and CASI was 70.07±18.50. We divided patients by CCA-IMT into two groups (CCA-IMT ≤ 0.87 mm and >0.87 mm). Compared with patients with CCA-IMT >0.87 mm, patients with CCA-IMT ≤ 0.87 mm had lower ICS (57±23% vs. 81±24%, $p=0.013$), similar initial CASI score (67.92±13.52 vs. 61.93±16.64, $p=0.28$) but higher CASI score at 3 months after stroke (77.36±14.12 vs. 63.69±19.89, $p=0.04$). In comparison, the improvement of CASI score at 3 months was significant higher in patients with CCA-IMT ≤ 0.87 mm (67.92±13.52 vs. 77.36±14.12, $p=0.001$) than those with CCA-IMT > 0.87 mm (61.93±16.64 vs. 63.69±19.89, $p=0.612$) (Table 1).

Correlation between the severity of ICS measured with WASID method and CCA-IMT value obtained dur-

Table 1. *Association of CCA-IMT, ICS and CASI scores*

	IMT ≤ 0.87 (n=14)	IMT > 0.87 (n=16)	*P*-value
Degree of ICS (%)	57±0.23	81±0.24	0.013*
CASI (0M)	67.92±13.52	61.93±16.64	0.275
CASI (3M)	77.36±14.12	63.69±19.89	0.041*
CASI (3M-0M), *P*-value	0.001*	0.612	

CCA-IMT: Common Carotid Artery Intima Media Thickness; ICS: Intracranial Arterial Stenosis; CASI: Cognitive Assessment Screening Instrument; (0M): At hospitalization; (3M): Three months post-stroke; (3M-0M): Improvement of score within the three months

*<0.05, t-test

Table 2. The general characteristics of patients stratified by CCA-IMT

	IMT ≤ 0.87 (n=14)	IMT > 0.87 (n=16)	*P*-value
Age [mean(S.D.)]	61.36 (10.7)	70.00 (8.4)	0.019*
Sex (male)	10 (33%)	11 (37%)	0.87
Hypertension	8 (27%)	11 (37%)	0.51
Diabetes Mellitus	2 (7%)	5 (17%)	0.27
Hyperlipidemia	1 (3%)	4 (13%)	0.19
Ischemic heart disease	0	1 (3%)	0.34
Smoking	4 (13%)	5 (17%)	0.87

*<0.05, Chi-square test for categorical data, *t*-test for continuous variables.

ing hospitalization (r = .51, $p=0.004$) and three months post-stroke (r = .49, $p=0.007$) were significant.

Older age was significantly associated with CCA-IMT (61.36±10.7 vs. 70.0±8.4; $p=0.019$). Gender and vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and smoking) were not associated with CCA-IMT (Table 2).

DISCUSSION

Our study found that among patients with first-ever ischemic stroke, those with lower initial CCA-IMT values had better CASI performance three months after stroke. All patients showed improvement in CASI performance at three months after stroke; however, only the group with lower CCA-IMT showed statistically significant improvement compared to the group with higher CCA-IMT. Despite the statistical significance, these results, based on a rather small sample, suggest a larger study for further exploration and validation. To our knowledge, most of the investigations of VCI focus on the trend beyond the period of six months to one year, therefore, we intend to investigate the trend of post-stroke cognitive change from the time of the patients' hospitalization to the third month after the stroke. Tallelli et al.[9] reported that increased CCA-IMT was associated with cognitive impairment 1 year after their first ischemic stroke. In a study of non-stroke population, Auperin et al.[14] reported that increased CCA-IMT was associated with compromised cognitive performance in a subgroup of male patients with carotid atherosclerotic plaques. Cerhan et al. and Knopman et al. found that CCA-IMT was associated with cognitive impairment in the baseline evaluation of non-stroke patients but no association was found 4 years later[15-16]. In our post-stroke patients, study results showed that the post-stroke cognitive impairment might be associated with increased of CCA-IMT - that was consistent with these earlier studies.

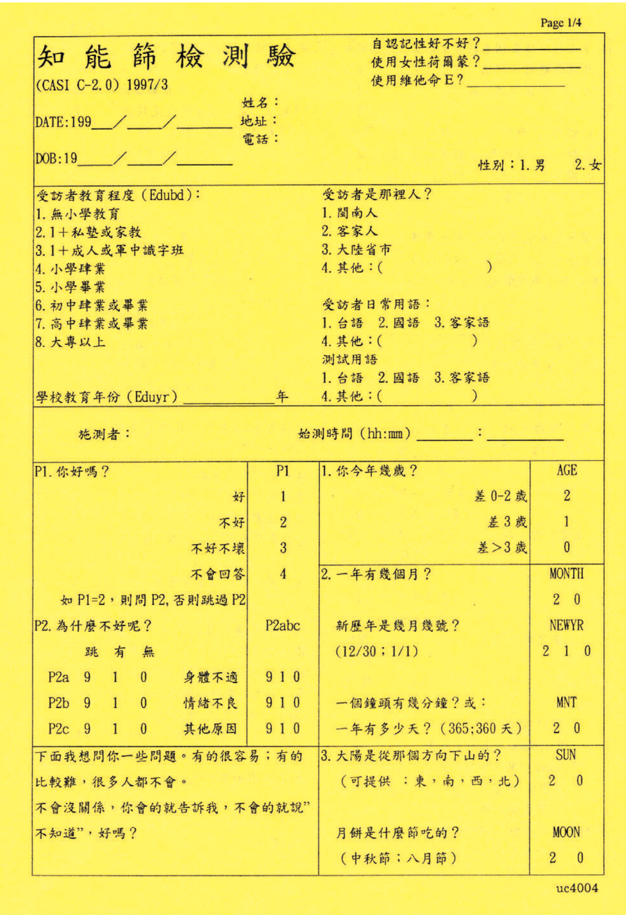
Another aspect of our findings is that stroke patients with the lower CCA-IMT values had less severe ICS compared to those with higher CCA-IMT. Establishment of methods for measuring the major ICS in a larger scale of study is necessary for further validation of the finding. CCA-IMT is associated both with stroke[6] and white matter lesions[1] and thus has been qualified as a marker of cerebral atherosclerosis. The cerebral atherosclerosis may be more severe in stroke patients with increased CCA-IMT values as our study showed, a condition that provided an additional risk of post-stroke cognitive impairment.

Age is a risk factor of cognitive impairment and increased CCA-IMT value[9,17]. In the present study, the CCA-IMT ranged from 0.38 to 1.27 mm, increases in CCA-IMT with age was variable from 0.009 mm per year from Japanese data[18] to 0.01 mm per year from US communities[19]. These studies might explain the significant association of higher CCA-IMT and older age in the groups studied. However, the correlation between the age and the initial CCA-IMT, initial CASI and ICS were not significant. Besides, the CCA-IMT values we obtained initially and at three months after stroke were similar (1.04±0.59 mm vs. 1.06±0.59 mm, $p=0.88$). These data suggest that a longer follow-up study beyond one year may be necessary if further exploration of the influence of age on CCA-IMT growth is desired in future studies. The patients with similar CCA-IMT after three months had their improvement in CASI performance generally, these results might imply that other factors beside age may affect post-stroke cognitive function. A larger population and longer term of investigation is needed for further validation of these findings.

The limitations of this study should also be considered. A larger scale of study will give a more powerful and less variable results to explore the association of CCA-IMT, VCI, ICS and the conventional vascular risk factors[20-22]. Assessment of cognition was based on CASI, which is a screening tool and not a diagnostic instrument. The use of more specific diagnostic tools is suggested for future studies. For the measurement of CCA-IMT, measurement of the far wall might be of less value for indication of an atherosclerotic process than measurement at multiple carotid sites. Moreover, establishment of methods for measuring the branches with narrow and tortuous segments, and having all the major ICS including bilateral ACA, MCA, PCA, VA and BA being measured are necessary in our future study. We intend to quantify the ICS by categorizing the ICS as mild, moderate and severe groups and have their association with the correlated variables instead of using ICS as a continuous variable because the sensitivity of MRA to detect a small percentage change of blood vessels lumens may not be reliable.

In conclusion, CCA-IMT was associated with the severity of ICS and VCI at three months after a first-ever ischemic stroke as shown in this study. The patients with lower CCA-IMT had a better CASI performance at three months after stroke. These results suggest a larger scale of study to explore the association of IMT, VCI and ICS three months (and later) after stroke, and help define the study design of any future study with an expanded sample size and more variables to explore.

APPENDIX



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知 能 篩 檢 測 驗
(CASI C-2.0) 1997/3

自認記性好不好？______
使用女性荷爾蒙？______
使用維他命E？______

姓名：
DATE:199___/___/___ 地址：
電話：
DOB:19___/___/___
性別：1. 男 2. 女

受訪者教育程度（Edubd）：
1. 無小學教育
2. 1＋私塾或家教
3. 1＋成人或軍中識字班
4. 小學肆業
5. 小學畢業
6. 初中肆業或畢業
7. 高中肆業或畢業
8. 大專以上
學校教育年份（Eduyr）______年

受訪者是那裡人？
1. 閩南人
2. 客家人
3. 大陸省市
4. 其他：(　　　)
受訪者日常用語：
1. 台語 2. 國語 3. 客家語
4. 其他：(　　　)
測試用語
1. 台語 2. 國語 3. 客家語
4. 其他：(　　　)

施測者：　　始測時間（hh:mm）____：____

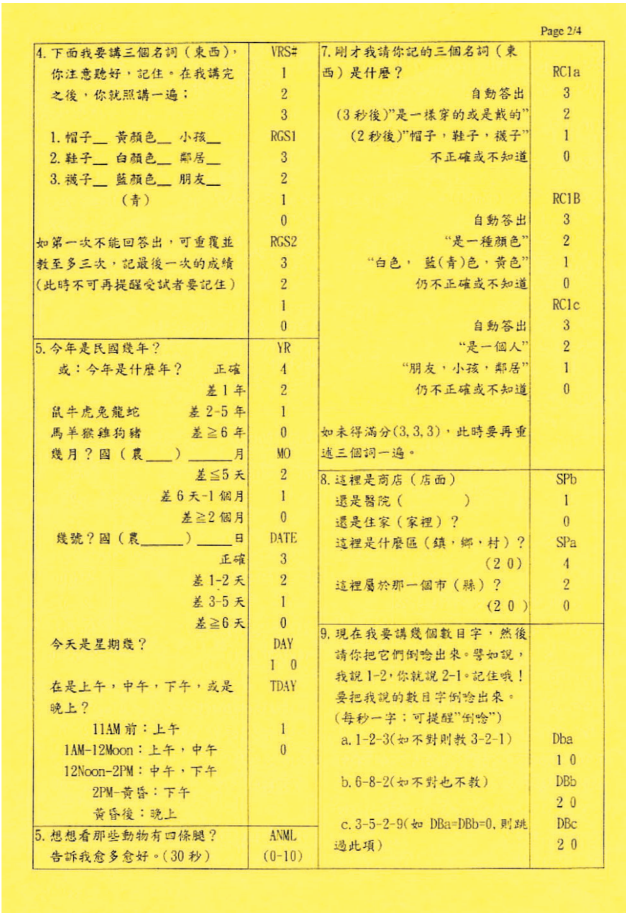
P1. 你好嗎？ — P1
好 1
不好 2
不好不壞 3
不會回答 4
如 P1=2，則問 P2, 否則跳過 P2
P2. 為什麼不好呢？ — P2abc
跳 有 無
P2a 9 1 0 身體不適 9 1 0
P2b 9 1 0 情緒不良 9 1 0
P2c 9 1 0 其他原因 9 1 0

1. 你今年幾歲？ — AGE
差 0-2 歲 2
差 3 歲 1
差>3 歲 0
2. 一年有幾個月？ — MONTH 2 0
新歷年是幾月幾號？(12/30；1/1) — NEWYR 2 1 0
一個鐘頭有幾分鐘？或：一年有多少天？（365;360 天） — MNT 2 0

下面我想問你一些問題。有的很容易；有的比較難，很多人都不會。
不會沒關係，你會的就告訴我，不會的就說"不知道"，好嗎？

3. 太陽是從那個方向下山的？（可提供：東，南，西，北） — SUN 2 0
月餅是什麼節吃的？（中秋節；八月節） — MOON 2 0

uc4004



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4. 下面我要講三個名詞（東西），你注意聽好，記住。在我講完之後，你就照講一遍； — VRS# 1 2 3
1. 帽子__ 黃顏色__ 小孩__
2. 鞋子__ 白顏色__ 鄰居__
3. 襪子__ 藍顏色__ 朋友__
(青)
RGS1 3 2 1 0
如第一次不能回答出，可重覆並教至多三次，記最後一次的成績（此時不可再提醒受試者要記住） — RGS2 3 2 1 0

5. 今年是民國幾年？ — YR
或：今年是什麼年？ 正確 4
差 1 年 2
鼠牛虎兔龍蛇 差 2-5 年 1
馬羊猴雞狗豬 差≧6 年 0
幾月？國（農___）___月 — MO
差≦5 天 2
差 6 天-1 個月 1
差≧2 個月 0
幾號？國（農___）___日 — DATE
正確 3
差 1-2 天 2
差 3-5 天 1
差≧6 天 0
今天是星期幾？ — DAY 1 0
在是上午，中午，下午，或是晚上？ — TDAY
11AM 前：上午 1
1AM-12Moon：上午，中午 0
12Noon-2PM：中午，下午
2PM-黃昏：下午
黃昏後：晚上
5. 想想看那些動物有四條腿？告訴我愈多愈好。(30 秒) — ANML (0-10)

7. 剛才我請你記的三個名詞（東西）是什麼？ — RC1a
自動答出 3
(3 秒後)"是一樣穿的或是戴的" 2
(2 秒後)"帽子，鞋子，襪子" 1
不正確或不知道 0
RC1B
自動答出 3
"是一種顏色" 2
"白色， 藍(青)色，黃色" 1
仍不正確或不知道 0
RC1c
自動答出 3
"是一個人" 2
"朋友，小孩，鄰居" 1
仍不正確或不知道 0
如未得滿分(3,3,3)，此時要再重述三個詞一遍。

8. 這裡是商店（店面）還是醫院（　　）還是住家（家裡）？ — SPb 1 0
這裡是什麼區（鎮，鄉，村）？(2 0) — SPa 4 2 0
這裡屬於那一個市（縣）？(2 0)

9. 現在我要講幾個數目字，然後請你把它們倒唸出來。譬如說，我說 1-2，你就說 2-1。記住哦！要把我說的數目字倒唸出來。（每秒一字；可提醒"倒唸"）
a. 1-2-3(如不對則教 3-2-1) — Dba 1 0
b. 6-8-2(如不對也不教) — DBb 2 0
c. 3-5-2-9(如 DBa=DBb=0, 則跳過此項) — DBc 2 0

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10. 第一次出錯時，記 0 分，但糾正之。需提醒時記 0 分。 連得兩個 0 分後中止。 100 塊錢用掉 3 塊，還剩多少錢 (97) 再用掉 3 塊，還剩多少錢(94) (再重覆三次) (91)(1 0) (88)(1 0) (85)(1 0)	SUBa 1 0 SUBb 1 0 SUBc 3 2 1 0	如果你把借來的傘弄丟了，你會怎麼辦？ 告知原主，道歉 (1 0) 賠償 (1 0) 如果你在路上看到別人遺失的身份証，你會怎麼辦？ 交給警察，派出所；寄回；其他適當有效作為 不去碰；其他次等作為 不適當之作為	JGTb 2 1 0 JGTc 2 1 0
11. 橘子和香蕉相同的地方是—它們都是水果。(停 2 秒) ____和____有什麼相同？ ____和____都是什麼？ 魚-蝦 海味，海鮮，水產 食品，水中之物.... 答錯或不知道 (教二分答案) 桌子-椅子 傢俱 四條腿，木製，吃飯用....... 答錯或不知道 手-腳 身體的一部份，四肢 五指(趾)，骨，肌肉........ 答錯或不知道	SIM1 2 1 0 SIM2 2 1 0 SIMA 2 1 0	13. 請你仔細聽我要講什麼。等我講完，你就一字不差地照講一遍。(停 2 秒) 他想要回去 (2.5 秒) 全對 錯漏一，二字 錯漏更多 下面請你照講；(5 秒) 這個黃杯子(1 0) 比紅飯碗 (1 0) 還要重 (1 0)	RPTa 2 1 0 RPTb 3 2 1 0
12. 如果你鄰居的房子失火了，你會怎麼辦？ (每類一分；可加問一次"還會做什麼？") 打 119，報警，通知消防隊 通知或救屋內的人 幫忙救火 通知其他鄰居 保全自家人財	JGTa 2 1 0	14. 我想請你做一件事 (出示卡片) 請閉上眼睛 會照著做 提醒了會做 會說不會做 讀做都不會	READ 3 2 1 0
		15. 模仿繪圖 (動筆時開始計時) a. O (15 秒) 大致封閉之圖形 長短直徑之比＞2:1 更差	DRWa 2 1 0

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b. ◇ (30 秒) 四邊並大致菱形 長短邊之比＞2:1；其他之封閉形 更差 c. (60 秒) 每個五邊形 大致正五邊形 4 4 長短邊之比>2:1 3 3 其他封閉圖形 2 2 不封閉，≧2 邊 1 1 ＜2 邊 0 0 交 叉 是四個角 2 非四個角 1 沒有交叉 0	DRWb 2 1 0 DRAW 10 9 8 7 6 5 4 3 2 1 0	19. [臉上]這〔部份〕叫什麼？ (每部份二秒) 額頭____下巴____肩膀____ 手掌 (掌心) ____大姆指____ 下面我要請你看幾樣東西... 這是什麼？ 湯匙 (調羹) ______ 硬幣 (銅板，錢幣) ______ 牙刷______ 鑰匙______ 梳子______ 自己原會及教了會重覆的名稱 (5-0)	BODY 5 4 3 2 1 0 OBJa 2 1 0 OBJb 3 2 1 0 RPNM
16. 我想看看你寫的字，請你寫人，父，母，子，女 (60 秒) 執筆方式 正確 不正確 執筆用手 右 左	WRITE (0-5) PEN 1 0 PENHD 1 2	20. 請你記住這五種東西。 (等 5 秒；蓋住；再問：) 我剛才給你看的是那五樣東西？ 匙______幣______刷______ 鑰______梳______	RCOJ 5 4 3 2 1 0
17. 遵循三段口示 請你用左 (右) 手來拿這張紙，(1 0) 用雙手把它對折一次，(1 0) 然後交還給我 (1 0)	CMD 3 2 1 0	結束時間：______：______ *請畫時鐘* 測驗耗時 (分鐘)	CASI TIME
18. 先前我要你記住的三個名詞 (東西)是什麼？ a. 穿戴：帽子，鞋子，襪子(3-0) b. 顏色：白色，藍色，黃色(3-0) c. 人：朋友，小孩，鄰居 (3-0)	RC2 a b c	分數效度 (可圈選數種) 有效 重聽 視覺不良 動作不良 方言不通 神智不清 身(心)不適 其他原因 (9 或 2→8) (9 或 2→8)	VLDT 1 2 3 4 5 6 7 8 VLDT2 VLDT3

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