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Relationships between ophthalmic artery flow direction and cognitive performance in patients with unilateral carotid artery stenosis

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A B S T R A C T

Background: Cerebral hypoperfusion is responsible for cognitive impairment in patients with severe carotid artery stenosis (CAS). The manifestation of reversed ophthalmic artery flow (ROAF) is not uncommon in patients with CAS, suggesting a state of intensified cerebral hypoperfusion. This study aimed to examine whether the presence of ROAF can exacerbate cognitive impairment in patients with severe unilateral CAS.
Methods: One-hundred-and-two patients with CAS and 37 age-matched volunteers participated in this case–control study. Depending on the side of CAS and occurrences of ROAF, the patients were allocated to four groups: left CAS groups with ROAF ($n = 28$) or without ROAF ($n = 22$), and right CAS groups with ROAF ($n = 26$) or without ROAF ($n = 26$). All subjects underwent a battery of neuropsychological tests.
Results: All patients performed worse than the control group on most tests. No significant differences were observed between patient groups (ps > 0.05), except for inferior performance on psychomotor speed and visuospatial tests in the right ROAF group (ps < 0.03). Hierarchical regression analyses indicated strong contributions of estimated premorbid intelligence to performance on most tests (ps < 0.05). The severity of left and right CAS was distinctively associated with different functions. To a lesser extent, the severity of infarcts was also associated with impairment of psychomotor speed and some executive functions (ps < 0.05). The contributions of ROAF to performance on most tests were negligible.
Conclusion: Patients with unilateral CAS may present with specific cognitive impairment relevant to the ipsilateral hemispheric functions. However, the manifestation of ROAF does not necessarily imply more extensive or severe cognitive impairment.

1. Introduction

Severe carotid artery stenosis (CAS) is associated with cognitive decline [1]. Chronic cerebral hypoperfusion is one of the major causes of cognitive impairment in patients with asymptomatic CAS [2], and cognitive improvement after carotid revascularization can be attributed to perfusion restoration [3]. Unilateral CAS may lead to asymmetric cerebral hypoperfusion and corresponding asymmetric amyloid plaque deposition patterns [4], and may even accelerate cognitive decline in patients with Alzheimer's disease [5]. Some studies have found that patients with right or left unilateral CAS may present different patterns of cognitive impairment [6], but not every study has yielded consistent results [7].

In patients with severe CAS, collateral blood supply from the circle of Willis and ophthalmic artery (OA) are important for the maintenance of adequate cerebral perfusion [8]. Reversed ophthalmic artery flow (ROAF) is associated with compromised cerebral hemodynamic brought about by intracranial artery stenosis and CAS, and is deemed as a steal phenomenon resulting from inadequate collateral cerebral blood supply [9]. Since hypoperfusion has been implicated in cognitive impairment in patients with CAS, it is possible that the presence of ROAF may not only signify more enhanced carotid stenosis and hence more profound intracranial blood insufficiency [10], but may also be associated with more severe cognitive impairment. Indeed, ROAF has been found to be associated with worse functional outcomes [11]. However, it is not known whether patients with ROAF may have worse cognitive performance than those with forward OA flow.

The study aimed to examine whether there are any specific cognitive deficits distinctively associated with left and right CAS and to investigate whether the presence of ROAF is associated with more pronounced impairment in patients with severe unilateral CAS.

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2. Methods

2.1. Subjects

One-hundred-and-two right-handed patients (aged between 46 and 83 years; 94 males, 8 females) with unilateral carotid artery stenosis from the Stroke Registry Dataset [12] of Linkou Chang Gung Memorial Hospital, Taiwan, were recruited to participate in this case–control study. They were enrolled based on the following inclusion criteria: (1) only the left or right internal carotid artery showed severe diameter stenosis (≥70%), and the stenosis of the contralateral carotid was ≤50% on angiography; (2) age was ≥45 years; (3) the literacy level was at least equivalent to the level of the 4th-grade pupils on the Chinese Graded Word Reading Test (CGWRT) [13]; (4) the score on the National Institutes of Health Stroke Scale (NIHSS) [14] was ≤8; (5) the score for the Barthel Index [15] was ≥80; (6) the score for the Modified Rankin Scale[16] was ≤3; (7) the duration between neuropsychological testing and the latest cerebrovascular attacks was more than 90 days. The exclusion criteria were: (1) a score on the Mini Mental Status Examination (MMSE) [17] score was ≤20; (2) a score on the Clinical Dementia Rating Scale (CDR) [18] was ≥1; (3) the presence of any expressive/receptive language disturbance; (4) a history of coronary artery bypass surgery; and (5) the presence of severe renal disease (serum creatinine >3 mg/dL) or undergoing hemodialysis therapy.

All patients were allocated to the left stenosis group (Lt-CAS, $n = 50$) or right stenosis group (Rt-CAS, $n = 52$), depending on the side of CAS over 70% while the opposite side had mild stenosis (≤50%) on angiography. Color-Coded Carotid Duplex (CCCD) showed 22 patients with left CAS had normal (forward) OA flow and 28 with ROAF; accordingly, they were divided into two groups: the Lt-OA-F and Lt-OA-R, respectively. Similarly, the patients with right CAS were assigned to the Rt-OA-F group ($n = 26$) and Rt-OA-R group ($n = 26$).

Thirty-seven volunteers (aged between 53 and 81 years; 32 males, 5 females) were recruited for the control group by advertisements placed in local hospitals and various local communities in northern Taiwan. None of them had a history of neurological disorder, psychiatric disorder or head injury. Their MMSE scores were all well above 25 points.

The Institutional Review Board, Linkou Chang Gung Memorial Hospital, Taiwan, approved the research protocol of this study. Prior to the enrollment, all subjects gave their written informed consent after the nature and the procedures of the study were explained in detail.

2.2. Cerebrovascular investigations

2.2.1. Carotid artery stenosis

The severity of CAS was determined on digital subtraction angiography (DSA) according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [19]. CCCD and brain magnetic resonance angiography were performed to determine the carotid artery stenosis severity in the control group.

2.2.2. OA blood flow

Peak systolic velocity and end diastolic velocity were measured in both ophthalmic arteries by CCCD. The OA was identified as the vessel parallel to the nasal border of the optic nerve just after crossing it. The sample volume was 0.5 mm in width; the sampling angle was adjusted to the vessels [20].

2.2.3. MRI acquisition and measurement

Axial T1-weighted sequence (spin-echo; repetition time [TR]/echo time [TE] = 449/12 ms; matrix 256 × 256), fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE/TI = 9416/90/2200) and diffusion-weighted sequence (single-shot spin-echo echo-planar technique; TR/TE = 2812/60; b values of 0, 500 and 1000 s/mm^2) were obtained using a 1.5-Tesla scanner (Symphony, Siemens) with 5-mm slice thickness and 0.5-mm inter-slice gap for each subject.

Trained neurologists, blinded to clinical and cognitive conditions, conducted the qualitative and quantitative measurements of MRI imaging as described in our previous study [21]. Lacunar infarcts were defined as lesions less than 15 mm in diameter with the same MRI signal characteristics as cerebrospinal fluid. The severity of cerebral infarct was visually rated as 0 = no lesion, 1 = one focal lesion (≥5 mm), 2 = more than one focal lesion, and 3 = confluent lesions [22].

2.3. Neuropsychological assessment

2.3.1. Reading abilities

As the formative education and dialects of elderly people in Taiwan are quite heterogeneous, the CGWRT was used to ensure all the subjects had minimal command of Chinese reading ability. The CGWRT comprises 200 single Chinese characters stratified into 10 levels of difficulty (school grades 0 to 9) according to their cumulative frequency in news materials [13].

2.3.2. Fluid intelligence

The Raven's Standard Progressive Matrices (RSPM) [23] was used to test current intellectual ability. The estimated premorbid RSPM (Est-RSPM) score was obtained for each subject by substituting age, years of education, and CGWRT score into the regression function provided by Chen et al. [24].

2.3.3. Memory functions

A Chinese16-word list learning test adapted from the California Verbal Learning Test-II (CVLT-II) [25], and the Brief Visual Memory Test-Revised (BVMT-R) [26] were used to assess the memory for verbal and visual materials, respectively.

2.3.4. Visuospatial functions

The Dot Counting and Position Discrimination subtests of the Visual Object and Space Perception battery (VOSP) [27] were used for screening visuospatial impairment.

2.3.5. Psychomotor speed

The Purdue Pegboard Test (PPT) [28] was used to test the manual dexterity for both hands.

2.3.6. Executive functions

The Category Fluency Test (CFT) and Design Fluency Test (DFS) of the Delis–Kaplan Executive System [29] were used to test the performance of response initiation and the ability to switch responding between different rules. The Stroop Test used for this study was similar to that described in MacNiven et al.'s [30] study. The stimuli were presented in red, yellow, green, or blue color on a LED screen attached to a Personal Computer for recording the reaction times (RTs) and the %correct responses. Subjects had to identify the color of a stimulus on the screen by pressing the corresponding button on a response box (20-cm wide). The stimuli were either "congruent" (color names and the colors of stimuli were the same), "neutral" (colored squares), and "incongruent" (color names were different from the colors of the stimuli). The Intra/Extra Dimensional Set Shift (IED) Test of the Cambridge Neuropsychological Test Automated Battery (CANTAB) [31] was used to test the flexibility of rule-governed choice.

2.4. Procedure

After the subjects had given their informed written consent, the cerebrovascular investigations and neuropsychological assessment were arranged. All investigations were completed within 2 weeks. All subjects underwent the neuropsychological assessment individually in two consecutive weekly sessions.