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Correlation between brain magnetic resonance imaging and blood inflammatory markers for patients with vascular cognitive impairment.

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Abstract

Objective: The aim was to research the correlation between brain magnetic resonance imaging and blood inflammatory markers for patients with varying degrees of vascular cognitive impairment.

Methods: Total 90 subjects were divided into vascular cognitive impairment with no dementia, vascular dementia and control group. The Chinese version of the Montreal Cognitive Assessment, Clinical Dementia Rating, activities of daily living scale and Hachinski Ischemic Scale were used for tests; the magnetic resonance imaging consisted of routine scanning sequences, susceptibility weighted imaging and diffusion tensor imaging; cardiopulmonary resuscitation, interleukin-6 and tumor necrosis factor-α were detected by enzyme-linked immunosorbent assay.

Results: Microbleeds mainly appeared under the cortex of frontal lobe and temporal lobe and in the basal ganglia, centrum semiovale, corona radiate and thalamus; the number of the microbleeding parts were larger than those of the vascular cognitive impairment with no dementia. The fractional anisotropy values in the parts under the cortex of frontal lobe and temporal lobe and in the basal ganglia, centrum semiovale, corona radiate and thalamus were lower than those of the vascular cognitive impairment with no dementia and the apparent diffusion coefficient values increased. Cardiopulmonary resuscitation, interleukin-6 and tumor necrosis factor-αlevel of the vascular dementia were higher than those of the vascular cognitive impairment with no dementia.

Conclusion: It was valuable for early diagnosis of vascular cognitive impairment and assessment of its severity to detect microbleeds by the susceptibility weighted imaging on magnetic resonance, examine Leukoaraiosis by the diffusion tensor imaging and the levels of serum inflammatory markers.

Keywords: Vascular cognitive impairment, Susceptibility weighted imaging, Diffusion tensor imaging, Inflammatory markers.

List of Non-Standard Abbreviations:

VCI: Vascular Cognitive Impairment; MoCA: Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; ADL: Activities of Daily Living; HIS: Scale and Hachinski Ischemic Scale; DWI: Diffusion Weighted Imaging; SWI: Susceptibility Weighted Imaging; DTI: Diffusion Tensor Imaging; CPR: Cardiopulmonary Resuscitation; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α; FA: Fractional Anisotropy; NINDS: National Institute of Neurological Disorders and Stroke; CSN: Canadian Stroke Network; SE: Spin-Echo sequence; TR: Repetition Time; TE: Echo Time; FOV: Field Of Vision; FA: Flip Angle; Min IP: Minimum Intensity Projection; SE EPI: Spin-Echo Echo Planar Imaging; ANOVA: One-Way Analysis Of Variance; LSD: Least Significant Difference; MRS: Magnetic Resonance Spectroscopy; BOLD-fMRI: Blood Oxygen Level Dependent functional MRI.

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Introduction

Vascular Cognitive Impairment (VCI), a kind of syndrome developed from mild cognitive impairment to dementia, is the second leading cause of senile dementia next to the Alzheimer's disease; due to its reversibility in the early stage, it is currently the only kind of dementia that can be prevented

[1]. With the acceleration of aging around the world, the incidence of cerebrovascular dementia is on the rise, which has seriously effect on the social adaptability of the patients; meanwhile, it is an important unfavourable factor for the full recovery of cerebrovascular diseases. At present, the diagnosis of VCI are still conducted based on clinical manifestations and neuropsychological scales, which are subjective for early clinical diagnosis and prevention [2].

Nowadays, various techniques were applied for early detection of disease. Parsian et al. optimized multi-Layer Perceptron Network (MLP) neural networks to Gray Wolf Optimization algorithm, and achieved significant achievements for melanoma detection [3]. Besides, based on defected and protruded structures, Razmjooy et al. explored a new distributed diode single-balanced mixer, the research might provide better development for disease detection [4,5]. Furthermore, Ghadimi et al. also designed a new low power rectenna for wireless sensor which was also closely related with detection of disease [5].

As in-depth researches on multiple sequences of the Magnetic Resonance Imaging (MRI), it is found that the VCI in the early phase is usually accompanied with Leukoaraiosis (LA) or Lacunar Infarction (LI), which is correlated with the occurrence and development of the disease [6]. However, routine examinations, such as Computed Tomography (CT) and routine sequences of MRI (T1, T2, DWI and fluid attenuated inversion recovery (FLAIR) sequences), only provide few information about the potential white matter tracts, and also have limited diagnostic value. Utilizing the diffusion anisotropy of water molecules to produce images, Diffusion Tensor Imaging (DTI) can sensitively reflect the structural changes of the brain white matter fibers and detect the exchanges of water molecules between components of the living tissue under pathological conditions [7]. In addition, cerebral microbleeds are remarkable risk factors of cognitive impairment of VCI patients. It is difficult to discover the microbleeds through routine examinations. However, Susceptibility Weighted Imaging (SWI) can form image contrasts *via* the difference of magnetic sensitivities between tissues and the amplitude image and phase image can be obtained at the same time. Detection rate of paramagnetic substances, including iron and hemorrhage products (deoxyhemoglobin and methemoglobin) is relatively higher. Moreover, the SWI sequence can display the hemorrhagic focus in a very sensitive way [8]. So far, there are still a small number of researches focusing on the correlation between the early diagnosis of VCI by SWI and DTI imaging and varying severities of illness.

The mechanism of VCI is possibly related to hypoxic ischemia, atherosclerosis, immune and inflammatory responses. Among them, the inflammatory responses play an important role in demyelinating lesions in the brain white matter which is featured by apoptosis and death of oligodendrocyte and loss of myelin protein [9]. Meanwhile, this research attempted to find inflammatory markers with higher sensitivity and specificity.

To sum up, the aim of this study was to research the correlation between brain magnetic resonance imaging and blood inflammatory markers for patients with varying degrees of vascular cognitive impairment. SWI and DTI were used in this study, and the expression of CPR, IL-6 and TNF-α were detected. This study may provide reference basis for early diagnosis of VCI and establishment of correlation with magnetic resonance imaging.

Materials and Methods

Object data

A total of 30 patients who were first diagnosed with VCI with no dementia and 30 with vascular dementia in our hospital from June, 2014 to June, 2016 were selected consecutively, and another 30 normal healthy volunteers were selected. The diagnosis and typing of VCI were set based on the standards proposed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) in 2006 [10]. The Chinese version of the Montreal Cognitive Assessment (MoCA), Clinical Dementia Rating (CDR), activities of daily living (ADL) scale and Hachinski Ischemic Scale (HIS) were used for examinations. The informed consents had been obtained in this research. The cognitive impairment caused by non-vascular diseases, such as traumatic stress and Alzheimer's disease was excluded. There existed factors influencing the scores and inflammatory responses. There were contraindications for magnetic resonance examinations.

In the group of VCI with no dementia, there were 18 men and 12 women; their age ranged between 58~83 y (66.5 ± 14.2); there were 12 patients with a history of stroke, 8 with hypertension, 6 with diabetes and 5 with cardiac diseases; 11 patients were smoking; the average year of education was 10.8 ± 3.6 y; the score of MoCA averaged out to 22.4 ± 4.5 points; the CDR was<1.0; the ADL scored at 21.5 ± 6.6 points on average and the average score of HIS was 5.8 ± 1.4 points. The group of vascular dementia was composed of 16 men and 14 women with age ranged between 56~85 y; the average age was 64.8 ± 15.6 y; the numbers of history of stroke, hypertension, diabetes and cardiac diseases were 13, 7, 8 and 4, respectively; there were 10 patients smoking; the average year of education was 11.2 ± 3.8 y; the average scores of the MoCA, CDR, ADL and HIS were 18.6 ± 4.4, 1.7 ± 0.5, 33.8 ± 7.2 and 8.5 ± 2.3 points, respectively.

There were 15 male and 15 female patients in the control group whose age range was 55~82 y old and averaged out to 65.8 ± 15.5 y; the numbers of history of stroke, hypertension, diabetes and cardiac diseases were 10, 5, 7 and 4, respectively; 9 people were smoking; the average year of education was 11.3 ± 4.3 y; the scores were as follows: MoCA ≥ 26 points; CDR=0; ADL<26 points and HIS=0. The scale scoring was completed by the same survey team that was trained strictly.

Magnetic resonance imaging

The Avanto 1.5 T MR scanner with standard phased array head coil of German Siemens was used and the version of the software was Syngo MR B15. The spin-echo sequence (SE) was used for routine scanning. Axial T1WI: repetition time (TR)=635 ms, echo time (TE)=23.4 ms; T2WI: TR=4600ms, TE=110 ms; DWI: TR=9602 ms, TE=117 ms; the section thickness was 5.0 mm and the gap was 1.5 mm. The time of collection was 4~5 min, the Field Of Vision (FOV)=250 mm × 250 mm, the matrix was 256 × 256, a total of 176 sections were scanned, the Flip Angle (FA) was 9° and the average number of excitation was 1.

For transverse SWI sequence: TR=49 ms, TE = 40 ms, FOV=230 mm × 230 mm; the matrix was 320 × 320 and the deflection angle was 20°; the bandwidth was 80 kHz, the phase encoding was in left-right direction and the collection factor 2.0 was executed; the section thickness was 2.0 mm, the gap was 0 and a total of 48 sections were scanned. The amplitude images and phase images obtained after the collection were processed by high-pass filtering, data overlaying and minimum intensity projection (Min IP) at the workstation and then the ultimate SWI images were formed. The positions observed covered the cortex, subcortical white matter, deep white matter, basal ganglia, thalamus, ventricle and extracerebral space.

The axial spin-echo echo planar imaging (SE EPI) sequence was used for DTI scanning and the acquisition time was 6~7 min; with TR=6000 ms and TE=90 ms, the section thickness was 3 mm and a total of 45 sections were scanned; the bandwidth was 150 kHz; FOV=240 mm × 240 mm; the matrix was 128 × 128 and the FA was 3°; the average number of excitation was 3; b value was 0 and the diffusion features were measured along 20 non-collinear directions. The scanning was located at the sagittal positions of 3D T1WI, the scanning baseline was horizontal and the range was the whole brain. The DTI analysis software package (Neuro 3D) at the workstation was applied to reconstruct the FA image, ADC image and b0 image, of which the red, blue and green colors on the FA image represented the fibers in left-right, up-down and anterior-posterior directions, respectively. The FA and ADC values were measured on regions of interest in different sections of the FA axial view; the positions and sizes of the voxels on both sides were substantially symmetric and those located around the cerebrospinal fluid were avoided; for bilateral frontal lobes, the interventricular foramen section and consecutive bilateral sections above it were selected; 2~3 voxels with an area of 30 mm^2 were placed in the white matter areas on each side of the frontal lobe in every section. The genu and splenium of corpus callosum were measured in three consecutive sections with one voxel in each section; the area of the voxel in the genu was 15 mm^2 and that in the splenium was 30 mm^2.

Serum inflammatory markers

The levels of CPR, IL-6 and TNF-α were tested by ELISA and the reagents were purchased from Jiangsu Beyotime Biotechnology Co., Ltd. The test was conducted according to the instructions. The levels were measured three times respectively and the mean values were calculated.

Statistical methods

SPSS 20.0 software was used for statistical analysis, the measurement data were presented as means ± standard deviations, the One-Way Analysis Of Variance (ANOVA) was used in comparison among groups, the least significant difference (LSD)-t test was used in pairwise comparison and the t test was used in comparison between two groups; the enumeration data were presented as cases or (%) and the χ^2 test was used in comparison between two groups; $p<0.05$ represented the differences were statistically significant.

Results

SWI image analysis

On the SWI images of the vascular dementia, the microbleeds mainly appeared under the cortex of frontal lobe and temporal lobe and in the basal ganglia, centrum semiovale, corona radiate and thalamus; the number and area of the microbleeding parts were significantly larger than those of the VCI with no dementia; there were no microbleeds detected in the control group (Table 1).

Table 1. *Comparisons of positions and areas of microbleeds on SWI images.*

Group	VCI with no dementia (n=30)	Vascular dementia (n=30)	Control group (n=30)	t/χ^2	p
Bleeding part (case (%))					
Under cortex of frontal lobe	5 (16.7)	12 (40.0)	0	4.022	0.045
Under cortex of temporal lobe	3 (10.0)	10 (33.3)	0	4.812	0.028
Basal ganglia	6 (20.0)	15 (50.0)	0	5.934	0.015
Centrum semiovale	5 (16.7)	13 (43.3)	0	5.079	0.024
Corona radiata	5 (16.7)	14 (46.7)	0	6.239	0.012
Thalamus	7 (23.3)	16 (53.3)	0	5.711	0.017

Average number (n)	0.8 ± 0.2	1.5 ± 0.4	0	5.632	0.016
Bleeding area (mm^2)	10.2 ± 3.3	26.5 ± 9.7	0	8.527	0

Table 2. *DTI image analysis.*

Group	FA value					ADC value				
	VCI with no dementia	Vascular dementia	Control group	f	p	VCI with no dementia	Vascular dementia	Control group	f	p
Under cortex of frontal lobe	0.48 ± 0.15	0.36 ± 0.09	0.76 ± 0.23	5.632	0.02	0.57 ± 0.12	0.86 ± 0.25	0.32 ± 0.09	6.325	0.013
Under cortex of temporal lobe	0.52 ± 0.16	0.39 ± 0.11	0.83 ± 0.25	5.527	0.023	0.46 ± 0.11	0.77 ± 0.19	0.35 ± 0.06	6.217	0.016
Basal ganglia	0.39 ± 0.14	0.27 ± 0.05	0.66 ± 0.20	5.348	0.027	0.49 ± 0.13	0.82 ± 0.24	0.28 ± 0.04	6.657	0.008
Centrum semiovale	0.50 ± 0.21	0.35 ± 0.12	0.84 ± 0.28	5.867	0.017	0.35 ± 0.09	0.69 ± 0.16	0.19 ± 0.03	6.358	0.011
Corona radiata	0.46 ± 0.18	0.33 ± 0.13	0.78 ± 0.24	6.231	0.011	0.37 ± 0.07	0.67 ± 0.15	0.24 ± 0.05	6.754	0.006
Thalamus	0.44 ± 0.17	0.25 ± 0.06	0.83 ± 0.27	6.157	0.015	0.34 ± 0.06	0.75 ± 0.18	0.16 ± 0.06	6.968	0.002

Table 3. *Comparisons of levels of serum inflammatory markers (μmol/L).*

Group	VCI with no dementia	Vascular dementia	Control group	f	p
CPR	7.8 ± 2.2	9.3 ± 3.5	5.2 ± 1.6	5.562	0.023
IL-6	87.5 ± 21.4	123.4 ± 56.3	45.6 ± 10.2	10.324	0
TNF-α	35.7 ± 8.9	78.6 ± 15.7	15.8 ± 3.4	21.536	0

DTI image analysis

On the DTI images of the vascular dementia, the FA values in the parts under the cortex of frontal lobe and temporal lobe and in the basal ganglia, centrum semiovale, corona radiate and thalamus were apparently lower than those of the VCI with no dementia and the ADC values increased greatly ($p<0.05$) (Table 2).

Analysis of serum inflammatory markers

The levels of CPR, IL-6 and TNF-α in serum of the vascular dementia were obviously higher than those of the VCI with no dementia and those levels were the lowest in the control group; the differences were statistically significant ($p<0.05$) (Table 3).

Discussion

SWI is highly sensitive to bleeding, venous blood and iron deposition and of significant value to qualitative diagnosis of vascular malformations, multiple intracerebral hemorrhages and microbleeds. The microbleeds are presented as uniform round or round-like low signal zones with a diameter of about 2~5 mm on the SWI sequence, without edema around. SWI can clearly indicate the position, number, size and boundary of the hemorrhagic focus, especially the cortex of frontal lobe and temporal lobe, basal ganglia, thalamus and other important parts; if the number of foci is ≥ 3, it can be used as an important predictor of hemorrhagic VCI [11,12]. It was concluded from this research that, on the SWI images of the vascular dementia, the microbleeds were mainly located under the cortex of frontal lobe and temporal lobe and in the basal ganglia, centrum semiovale, corona radiate and thalamus; the number and area of the microbleeding parts were significantly larger than those of the VCI with no dementia; there were no microbleeds detected in the control group. Similarly with the study of Shams et al., microbleeds and their related clinical parameters are different among varying MR imaging sequences [13]. Moreover, Qiu et al. also confirmed that microvascular damage and cerebral microbleeds were closely related with vascular cognitive impairment [14]. A high microbleed count was with increased relationship with risk of cognitive deterioration [15]. The microbleeds could destroy the cortex of frontal lobe and the fiber connection of subcortical structure, having great influence on language, abstract thinking, higher intellectual activities and affective activities [16]. Distinct memory impairment might occur when the temporal lobe, particularly the hippocampus-involved memory circuit, was injured [8]; the diseases of the basal ganglia and thalamus could mainly lead to connection integrity of white matter tracts of the thalamus-cortex, inhibit the functions of the cortex of frontal lobe and temporal lobe on the same side and damage the Papez-Ston memory circuit that the thalamus was involved in [17].

The FA values on the DTI images mainly reflect the integrity of the fiber bundle structure and the ADC values indicate the

diffusion degree of free water. The white matter injury is generally manifested as drop of FA value and rise of ADC value. The study found that the FA value and ADC value of the white matter in the whole brain of VCI patients were significantly different from those of the healthy people and they were remarkably correlated with the decline of memory, attention and executive functions [18]. Naik et al. processed diffusion tensor imaging and confirmed that there was a closely relation between FA and extent of frontal lobe symptoms in the frontal lobes [19]. Using the index of DTI data of severity, the subjects with AD and normal controls could be separated significantly [20].This study concluded that, on the DTI images of the vascular dementia, the FA values in the parts under the cortex of frontal lobe and temporal lobe and in the basal ganglia, centrum semiovale, corona radiate and thalamus were significantly lower than those of the VCI with no dementia while the ADC values increased obviously. The injury of white matter beside the ventricle was related to cognitive decline and the injury of white matter under the cortex might have a correlation with late-onset depression [21]. Moreover, it was discovered in the research that DTI could not only detect the destruction of fiber integrity in the high signal zone of the brain white matter, but also find out the occult injuries existing in the normal-appearing brain white matter in vicinity; those occult injuries were also important causes of cognitive impairment [22].

Furthermore, Magnetic Resonance Spectroscopy (MRS) and blood oxygen level dependent functional MRI (BOLD-fMRI) are widely applied in degenerative changes of the brain [23,24]. The peripheral inflammatory markers of the VCI patients were analyzed during the research. It was concluded that the levels of CPR, IL-6 and TNF-α in serum of the vascular dementia were obviously higher than those of the VCI with no dementia and those levels were the lowest in the control group. Moreover, it suggested that the elevated levels of CPR, IL-6 and TNF-α may be significant for the guidance of VCI diagnosis. As shown in previous study, inflammation was a common phenomenon with expression change of IL-1β, IL-6 and TNF-α in different VCI subtypes [25]. The inflammation hypothesis of VCI stated that, under hypoxic ischemia conditions, the inflammatory responses mediated by microglial over-activation could destroy the blood-brain barrier, cause injury of brain white matter and promote the occurrence and development of vascular cognitive impairment [26-28].

Conclusion

Detecting microbleeds by the SWI on magnetic resonance and examining leukoaraiosis by the DTI and combine with the levels of serum inflammatory markers is of great value for early diagnosis of VCI and assessment of its severity to.

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