

Study on the clinical application of the MRS in the cognitive assessment after stroke

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Abstract. – OBJECTIVE: To discuss the value of the application of the magnetic resonance spectroscopy (MRS) in the assessment of cognitive function impairment and the observation of therapeutic effect.

PATIENTS AND METHODS: 30 patients with cognitive impairment after stroke (cognitive impairment group) and 30 patients with no apparent cognitive impairment (control group of the stroke) were selected through the screening of the mini-mental state examination (MMSE) scale, and another 30 healthy volunteers were selected (control group of the health). The general information of gender, age, education degree, disease duration and so on was matched among the 3 groups. MRS examined all the patients of the 3 groups at the time of enrollment, and the patients of both cognitive impairment and control groups received another assessment 2 months after treatment.

RESULTS: The NAA/Cr (N-acetyl aspartate/creatine) of the bilateral hippocampus of the cognitive impairment group was lower than those of both control group of stroke and health ($p < 0.05$), while the Cho/Cr was higher ($p < 0.05$). After treatment, both patients of the cognitive impairment group and the control group of the stroke experienced an increase of NAA/Cr and a decrease of Cho/Cr ($p < 0.05$).

CONCLUSIONS: MRS is applicative in the assessment of the cognitive impairment degree of the stroke patients and can also effectively identify the existence of the cognitive impairment, which makes it preferably valuable in the clinical application.

Key Words:

Stroke, Cognitive impairment, Magnetic resonance spectroscopy (MRS).

Introduction

Cognitive impairment after stroke, with relatively high incidence, has severely influenced the quality of surviving of patients and increased the

burden of the society¹⁻³. At present, the assessment of the cognitive impairment relies on the variety of cognitive function scales, but the results are lacking of objectivity because they are prone to be affected by the education degree of the patients. Besides, the patients of aphasia, severe cognitive and comprehensive impairment are unable to be assessed effectively. So there are still certain limitations on the clinical application for them. Yet, today, MRS is a unique noninvasive imageological technology for the research of the metabolic change of viable tissues and organs that can also conduct quantitative analysis on some chemical compounds⁴. It is then possible to study the cognitive impairment after stroke from the aspect of cerebral metabolism, which has characteristics of stability, repeatability and avoids the influence of language and education. For these reasons, MRS was applied in the cognitive function assessment of patients of different cognitive levels in the current study, and the changes before and after treatments were observed, in order to discuss the value of application of MRS on the assessment of the cognitive function and the observation of curative effect of the stroke patients.

Patients and Methods

Patients

Inclusive criteria of the disease group:

1. The stroke attacked firstly, and the diagnosis met the criterion revised in the fourth national stroke meeting of 1995, and was confirmed by head CT or MRI;
2. There was complaining of cognitive impairment by the patient him/herself or others representing him/her;

3. The subjects were with clear consciousness and stable condition and were able to coordinate in every test;
4. The subjects and/or their guardians were informed and consented the test and signed the agreement papers.

Exclusive criteria:

1. There was existing cognitive defects or suspicious cognitive impairment, like history of mental disorder, mood disorder, heavy drinking or drug abuse;
2. There were other cerebral organic diseases and severe functional damage of heart, lung, kidney, liver and so on;
3. Patients unable to finish the test because of severe visual or hearing impairment.

Patients suffering a stroke that had been hospitalized in the Rehabilitation Department of Xuzhou Center Hospital from June 2013 to June 2015 and missing the inclusive and exclusive criteria were selected and established as the disease group. According to the scoring standard diagnosing cognitive impairment of MMSE scale, the patients were further divided into 2 groups of 30 patients each, including the cognitive impairment group (patients with cognitive impairment) and the control group of the stroke (patients with no apparent cognitive impairment). This study was approved by the Ethics Committee of Xuzhou Center Hospital. Signed written informed consents were obtained from all participants before the study.

The Cognitive Impairment Group

The scores of the patients were under the standard score. There were 21 males and 9 females; the age range was 42-75 years and the mean age was (58.98 ± 9.17) years. 17 patients were with cerebral hemorrhage and 13 patients were with cerebral infarction. The control group of the stroke: the scores of the patients were above the standard score. There were 22 males and 8 females; the age range was 46-71 years and the mean age was (59.13 ± 8.55) years. 18 patients were with cerebral hemorrhage and 12 patients were with cerebral infarction.

Inclusive criteria of the control group of the health:

1. No complain of cognitive impairment by the patient him/herself or others representing him/her, and the MMSE score was normal;
2. No disease history of central nervous system (including brain trauma, cerebral vascular accident and so on);

3. No history of drug dependence and alcohol dependence, no history and family history of mental disorders and so on;
4. No abnormality by the test of nervous system;
5. The objects were informed and consented the test and signed the agreement papers.

30 healthy volunteers (including families or accompanies of the patients, and healthy physical examinees) being coincident with the patient group and the inclusive criteria were selected and established as the control group of the health, including 23 males and 7 females; the age range was 45-73 years and the mean age was (60.43 ± 7.7) years.

The objects of the 3 groups were all right handed. Through the analysis and comparisons on the general information of gender, age, education degree and so on, there were no significant differences among groups ($p > 0.05$) and they were comparable.

Study Methods

MMSE and MRS examined all patients of the 3 groups in the first 3 days of inclusion, and the patients of the cognitive impairment group and the control group of the stroke was re-examined after 2 months of rehabilitative treatment. The assessment of the scales was conducted by the same rehabilitative physician or therapist with the same standard, and the rehabilitative physician conducting assessment would not be involved in the rehabilitative therapy.

MMSE Assessment

There were 30 items in the MMSE scale, totally scoring 30. The contents include 6 aspects of orientation capacity (10 items), memory (6 items), attention and calculation capacity (5 items), language (4 items), executive capability (4 items) and visual space structural skill (1 item). The diagnostic standard of MMSE: score ≥ 17 indicated illiteracy (uneducated), score ≥ 20 indicated primary school education (educated time ≤ 6 years), score ≥ 24 indicated middle school education and above (educated time > 6 years). Patients under the standard score were considered to have cognitive impairment. This scale was used for the primary screening and grouping of the cognitive impairment in this study.

The MRS Examination

The achieve 3.0T superconductive MRI scan system of PHILIPS Corporation (Philips, Eindhoven, Netherlands) was applied for the MRI

head plain scan of all the subjects, including T1WI and T2W2 of T sect, T1WI of sagittal view and T2W2 of coronal view, using the standard head coil as emitting and receiving coil. The scanning parameters: T1WI time of repetition (TR) 2025.00 ms, time of echo (TE) 8.40 ms; T2WI time of repetition (TR) 4000.00 ms, time of echo (TE) 111.50 ms; matrix 320×192 , visual field $24.00 \text{ cm} \times 18.00 \text{ cm}$, layer thickness 6.00 mm, layer distance 1.00 mm. Axial T2WI TR 5000 ms, TE 120 ms, layer thickness 5 mm, layer distance 1.00 mm, number of stimulation (NSA) 2. Axial enhanced scan of inversion recovery (IR) sequence, TR 2400 ms, TE 24 ms, T 1860 ms, layer thickness 5 mm, distance 1.0 mm, FOV $24 \text{ mm} \times 24 \text{ mm}$, NSA1. The point-resolved selective spectroscopy (PRESS) was applied for the 1H-MRS test, with 3-dimensional multi-voxel spectrum collection. Time of repetition (TR) 1015 ms, time of echo (TE) 144 ms, field of view (FOV) 180 mm (front and back) $\times$ 162 mm (left and right) $\times$ 60 mm (head and foot), voxel = 18 mm (front and back) $\times$ 16 mm (left and right) $\times$ 12 mm (head and foot), number of stimulation (NSA) 1. The region of interest (ROI) was located in the parenchymal field of the bilateral hippocampus. Automatic baseline calibration, shimming and water suppression were completed firstly in the selected ROI by MR scanner, which leads to automatic spectrum collection scanning after the peak width at half height of water was less than 10 Hz. The head of the patient must keep steady to avoid the shadow. The examination and calculation of the metabolin by 1H-MRS: the metabolin examined by 1H-MRS included N-acetyl aspartate (NAA), Choline (Cho) and Creatine (Cr). The chemical frequency excursion positions of AA, Cr and Cho were 2.02 ppm, 3.03 ppm and 3.2 ppm respectively. The MRI scanner automatically completed the signal averaging and metabolin recognition after spectrum collection. The area under the wave crest of each metabolin, as well as the ratios including NAA/Cr and Cho/Cr were calculated.

The Curative Method of the Cognitive Impairment After Stroke

Corresponding drugs were given to both cognitive impairment and control groups of stroke for symptomatic treatment, including blood pressure and blood glucose control. Brain function and blood circulation were improved for the symptomatic support of drugs. Meanwhile, conventional rehabilitation training was applied to

all patients, like normal limb positioning in the early stage, preservation training of the motion range of joint, training of equilibrium function (including sit, stand and equilibrium training), training of body position transferring, gait training (including trainings of walk, go upstairs and downstairs and so on), training of hand function and occupational therapy, etc. Beside, according to the different results of the cognitive impairment assessment, the corresponding and one-to-one individual cognitive function training were given to every patient, including the function recovering training of disorientation, memory, disturbance of attention, calculation capacity, language and communication disturbance and thinking disturbance. The above training was conducted for 30 minutes every time, once a day and 5 times a week, lasting 2 months in all. Difficulty could be increased and the items could be altered for all the training, depending on the performance of patients. It was not necessary to finish all the training in a day; 2-3 items could be selected to train every day and repeated under the instruction of families in the ward or at home for the rest of the time.

Statistical Analysis

SPSS16.0 (Version X; IBM, Armonk, NY, USA) was used for the statistical processing of data. The χ^2 -test was applied for the comparison of qualitative data. Quantitative data were presented as means $\pm$ deviations ($\bar{x} \pm s$), and the data thus obtained were applied the normality test and the homogeneity test for a variance. Based on the characteristics of data obtained, those met the requirement were applied variance analysis for the comparison among 3 groups, individual sample *t*-test for the comparison between 2 groups, pairing *t*-test for the self-contrast and non-parametric test for those who could not meet the requirement. $\alpha = 0.05$ being the standard of the test, $p < 0.05$ suggested that the difference was statistically significant.

Results

Comparison of the MMSE Scores

The MMSE score of the cognitive impairment group before treatment was (16.77 ± 3.15) , while that of the control group of the stroke was (27.40 ± 2.14) and the control group of the health was (28.93 ± 1.36) . The score of the cognitive impairment group was prominently lower ($p < 0.01$) than that

of the other two groups. The score of the control group of the stroke was very significantly lower ($p < 0.01$) than that of the control group of the health. After 2 months of treatment, the MMSE score of the cognitive impairment group was (19.33 ± 4.01), and compared with that before treatment, the difference was statistically significant ($p < 0.01$). The MMSE score of the control group of the stroke was (19.33 ± 4.01), and compared with that before treatment, the difference was statistically significant ($p < 0.05$); compared with that of the control group of the health, the difference was not statistically significant ($p > 0.05$).

Comparisons of the MRS of the Cognitive Impairment Group and the Control Group of the Stroke Before and After Treatment

The bilateral NAA/Cr of the cognitive impairment group before treatment was very significantly lower ($p < 0.01$) than that of the control group of the stroke, while the bilateral Cho/Cr was very significantly higher ($p < 0.01$). The bilateral NAA/Cr of the control group of the stroke was very lower ($p < 0.01$) than those of the control group of the health, while the bilateral Cho/Cr was very higher ($p < 0.01$). After 2 months of treatment, the bilateral NAA/Cr of the cognitive impairment group was still significantly lower ($p < 0.05$) than those of the control group of the stroke and the control group of the health. The bilateral NAA/Cr of the cognitive impairment group was prominently higher ($p < 0.05$) than those before treatment, while the bilateral Cho/Cr was prominently lower ($p < 0.05$). After treatment, the bilateral NAA/Cr of the control group of the stroke was higher than those before treatment, while the Cho/Cr was lower, and the differences were statistically significant ($p <$

0.05); but being compared with the control group of the health, the difference was not statistically significant ($p > 0.05$) (Table I).

Discussion

Magnetic resonance spectroscopy (MRS) is a method, which utilizes the magnetic resonance phenomena and the chemical shift for the analysis on a series of specific nucleuses and their chemical compounds, and the most widely applied at present is hydrogen proton magnetic resonance spectroscopy (1H-MRS)^{5,6}. MRS is the only noninvasive examination method for the observation of the cellular metabolism of living body today⁷. As well, it is able to detect the biochemical metabolism of the tissues and organs and make a quantitative analysis of the compounds and thus provides new method of the diagnosis of the abnormal biochemical metabolism of all kinds of diseases on the molecular level.

The cerebral metabolites can be detected by MRS include N-acetyl aspartate (NAA), choline-containing compounds (Cho), creatine (Cr) and so on. Compounded by acetyl coenzyme and asparaginic acid, NAA mainly exists in the neuron, axon and dendrite, and is the generally acknowledged marker of the integrity, density and activity of the neuron⁸, the decrease of which usually being considered as neuron loss or dysfunction^{9,10}. The participation of Cho in the composition of the cell membrane is related to the metabolism of cell membrane phospholipids, and the rising of the Cho crest indicates activity of the cell proliferation, degradation of medullary sheath and increase of cholinergic neurotransmitter¹¹. Cr mainly consists of creatine and phosphocreatine, the dose of the volume of the

Table I. The MMSE scores of the 3 groups and the ratio of each item of the MRS ($\bar{x} \pm s$).

Group	Case	MMSE score	NAA/Cr of the left	NAA/Cr of the right	Cho/Cr of the left	Cho/Cr of the right
Cognitive impairment group	30					
Before treatment		$16.67 \pm 3.13^{a,b}$	$1.03 \pm 0.20^{a,b}$	$1.06 \pm 0.17^{a,b}$	$1.33 \pm 0.17^{a,b}$	$1.32 \pm 0.16^{a,b}$
After treatment		19.33 ± 4.01^c	1.15 ± 0.23^c	1.15 ± 0.16^c	1.26 ± 0.13^c	1.26 ± 0.12^c
Control group of the stroke	30					
Before treatment		27.40 ± 2.14^b	1.27 ± 0.13^b	1.25 ± 0.12^b	1.18 ± 0.11^b	1.17 ± 0.08^b
After treatment		28.47 ± 1.55	1.34 ± 0.12	1.33 ± 0.08	1.07 ± 0.09	1.06 ± 0.07
Control group of the health	30	28.93 ± 1.36	1.36 ± 0.10	1.37 ± 0.09	1.06 ± 0.09	1.05 ± 0.06

Note: Compared with the control group of the stroke before treatment, ^a $p < 0.01$; compared with the control group of the health, ^b $p < 0.01$; compared with that before treatment in the group, ^c $p < 0.05$.

two always being constant. Because the change of its content is independent on the decrease of the age and cognition, it is usually used as an internal standard for the standardization of other metabolites¹¹.

There are 3 most prominent spectral lines in the 1H-MRS of the normal human brain, which are resonance peaks of NAA-CH₃, PCr/Cr-N (CH₃) and Cho-N (CH₃) methylene proton. The analysis of the tissue metabolism changes is based on the content of the metabolite, so the abnormality of cellular structure and metabolite would be certified by the biochemical changes and the different crest value and ratio manifested in the 1H-MRS curve when the concentration of metabolite changed in certain degree, thus exerts the effect of diagnosing and assessing the disease.

In our study, the NAA/Cr of the bilateral hippocampus of the cognitive impairment group was prominently lower than that of the control group of the stroke and the control group the health, while the Cho/Cr was prominently higher, and the differences were statistically very significant ($p < 0.01$). It was suggested that there were degenerated changes of the nervous cells and axon in the hippocampus of the patients of the cognitive impairment group, which led to the damage and absence of the neuron and axon, as well as the dysfunction of the hippocampus¹². Besides of that, the hyperplasia of some gliocytes in the brain tissues also contributes to the increase of the Cho of hippocampus¹³. In the control group of stroke in our study, which was a group of patients complaining or being complained to have cognitive impairment, but were denied by the neuropsychological scale. The NAA/Cr of the bilateral hippocampus was lower than that of the control group of the health, while the Cho/Cr was higher, and the differences were statistically significant ($p < 0.05$), suggesting that there is a diagnostic value of MRS on the mild cognitive impairment in the early stage. This is consistent with previous findings¹⁴, but the specific effect of the assessment is still needed to be further studied with larger samples.

The theory of brain plasticity is the important theoretical base of the cognitive rehabilitation treatment after the central nervous system damage. The synaptic reconnection is considered as an important constitution of it¹⁵. It is the important theoretical base of the functional rehabilitation after the cerebral injuries brought by stroke, cranio-cerebral trauma and so on.

Luria¹⁶ believed that the facilitation and function of inhibition of the nerves could be conducted in a new way by the undamaged brain tissues through the functional reorganization. Based on that theory, multiple treatment methods have been created in order to remedy the skill loss caused by brain damage. The results of our study showed that the NAA/Cr of the bilateral hippocampus of the cognitive impairment group and the control group both experienced increase compared with those before treatment, while the Cho/Cr both decreased, and the differences were statistically significant ($p < 0.05$). These results indicated that there were certain improvements on the cognitive function after the stroke patients with cognitive impairment received comprehensive treatment, and MRS can effectively determine that.

At present, the neuropsychological scale is the most commonly used assessment for the diagnosis of cognitive impairment in the clinic, but the scale detection is subjective in some circumstances and it tends to be seriously influenced by the education degree of the objectives. It also has difficulties in the assessment of the patients of aphasia (especially the sensory aphasia, complete aphasia and so on), extremely poor visual acuity or the blind, the deaf, the brachial diplegia, severe cognitive impairment, and those who cannot concentrate for more than 5 minutes. The disadvantage of strong objectivity of the neuropsychological scale can be remedied by MRS, an imageological examination with completely no trauma, which brings less pain to the patients and is uninfluenced by the education degree, severe aphasia and dementia. Its advantages of good objectivity and repeatability can also make up.

Conclusions

The examination of MRS can objectively assess the cognitive impairment, evaluate the existence of the cognitive impairment, assess the curative effect and discover the vascular cognitive impairment. The application of MRS has fundamental clinical significance for the patients who cannot cooperate with the assessment of the scale on the early, simple, comprehensive and subjective assessment of cognitive impairment, and has preferably higher clinical application value to the perfection of the diagnosis of cognitive impairment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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