MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2014; 20: 1525-1530
DOI: 10.12659/MSM.892137

Received: 2014.07.31
Accepted: 2014.08.05
Published: 2014.08.27

Glucose Metabolism Measured by Positron Emission Tomography is Reduced in Patients with White Matter Presumably Ischemic Lesions

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF Jian Li
AG Wenli Hu

Department of Neurology, Beijing Chaoyang Hospital (Xi District), Capital Medical University, Beijing, China

Corresponding Author: Wenli Hu, e-mail: deepwater1985@163.com
Source of support: This work was supported by the National Natural Science Foundation of China (NSFC), China (No.81271309), and by the Beijing Natural Science Foundation, China (7132070)

Background: The severity and progression of white matter ischemic lesion (WMIL) are closely linked to vascular dementia. The function of neural tissue is closely linked to glucose consumption as the most important energy-supplying metabolic process. At present, ^{18}fluorine-fluorodeoxy glucose (^{18}FDG) positron emission tomography (PET) can provide regional and 3-dimensional quantification of glucose metabolism in the human brain. Although MMSE and MoCA are commonly used screens in cognitive impairment, no research team has yet validated their performance in WMIL. The purpose of our study was to compare MMSE and MoCA in screening for cognitive impairment and to explore the correlations between CMRglu values and executive function.

Material/Methods: All the participants underwent comprehensive clinical, MoCA, MMSE, MRI, and PET examinations. Patients in the WMIL group were subdivided into 3 severity subgroups according to the Fazekas scale.

Results: The MoCA scores were lower in the WMIL group. Our research indicates that MoCA is a more sensitive screening tool than the commonly used MMSE in detecting cognitive impairment in patients with WMIL. CMRglu values of gray matter were decreased in the WMIL group. Reductions of CMRglu in parietal lobe, frontal lobe, and white matter centrum semiovale were observed to different degrees in the WMIL groups according to the modified Fazekas scale. A significant negative correlation was found between executive function and CMRglu in the frontal lobe.

Conclusions: MoCA appears to be a more sensitive screening tool than the commonly used MMSE in detecting cognitive impairment in patients with WMIL. CMRglu can potentially be used as a biomarker for predicting the severity of WMIL.

MeSH Keywords: Leukoaraiosis • Mild Cognitive Impairment • Positron-Emission Tomography

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/892137

2043 4 6 27

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

White matter ischemic lesion (WMIL) is commonly seen in the elderly [1]. In WMIL patients, cognitive impairment adversely influences daily living activities and quality of life [2] while increasing caregiver burden [3]. The cerebral glucose metabolism decrease may reduce white matter integrity due to tissue damage or indirectly as a consequence of anterograde Wallerian and/or retrograde axonal degeneration [4]. Furthermore, reduced white matter integrity has been found to be associated with cognitive impairment [5]. The severity and progression of WMIL are closely linked to vascular dementia (VaD). In most Western countries, VaD makes up at least 10–20% of dementias, and in some Asian countries it is the most common form of dementia [6,7]. The function of neural tissue is closely linked to glucose consumption, which is the most important energy-supplying metabolic process [8]. Over the past few years, positron emission tomography (PET) has contributed much to the understanding of neurological disorders [9]. With this technique, the effects of glucose consumption on regional disturbances and changes in functional activity can be detected. At the present time, PET can provide regional and 3-dimensional quantification of glucose metabolism in the human brain [10,11]. Using measurements of the concentration of an injected radiolabelled glucose analog in small volumes of tissue along with appropriate reconstruction algorithms, computed tomographic images of the spatial tracer distribution can be obtained [12].

Our study investigated the correlation between cognitive function and cerebral metabolic rate for glucose utilization (CMRglu) by using dynamic ^{18}fluorine-fluorodeoxy glucose (^{18}FDG) PET imaging technology. The purpose of our study was to explore clinical and neuropsychological evidence for early detection of WMIL. We tested the following hypotheses: a) WMIL patients will show impairment in cognitive and executive function components, b) Patients with WMIL will show lower CMRglu values as compared to case controls, and c) There would be a correlation between CMRglu values and executive function.

Material and Methods

Study subjects

A prospective case-control study was designed. The study was conducted in the Department of Neurology, Beijing Chaoyang Hospital, Capital Medical University. In our study, 30 WMIL patients and 30 healthy older people were recruited consecutively during a 10-month period (March 1 to December 31, 2013). The 2 groups were matched for age, sex, and level of education. To be included, subjects had to be between the ages between of 60 and 80 years; have some degree of white matter hyperintensity on MRI; had to have no or only mild disability as determined by the Instrumental Activities of Daily Living Scale [13,14]; and had to sign an informed consent. Exclusion criteria were [14]: likelihood of dropping out because of the presence of severe illness (e.g., cardiac, hepatic, or renal failure, cancer or other relevant systemic diseases); severe unrelated neurological diseases; leukoencephalopathy of nonvascular origin (immunological, demyelinating, metabolic, toxic, infectious, other); severe psychiatric disorders; dementia (any type, determined from the medical record); identified as having had other confounding conditions that might have independently produced cognitive impairment; inability to provide informed consent; and inability or refusal to undergo PET.

Informed consent with written documentation was obtained from participants with co-signature from a legally authorized representative. The study was approved by the Human Research Protection Office and the Radioactive Drug Research Committee of Beijing Chaoyang Hospital, Capital Medical University.

Procedure and imaging acquisition

All the participants underwent comprehensive clinical and neuropsychological examinations, and 3.0-T MRI. Patients in the WMIL group were subdivided into 3 severity subgroups according to the Fazekas scale. Furthermore, all patients involved in our research were subjected to ^{18}FDG. Following that, the PET images were obtained. CMRglu was evaluated with semi-quantitative method by calculating the cerebral glucose standard uptake value (SUV) [15].

Cognitive assessment

The subjects' cognitive function was evaluated with the Chinese versions of the Mini-Mental State Examination (MMSE) [16] and Montreal Cognitive Assessment (MoCA) [17]. We gave the MMSE and MoCA on the same day to the subjects, ranging in age from 60 to 80 years, stratified by decade. Half took the MMSE first, and half took the MoCA first. We subsequently gave them trail making tests A and B (TMT-A, TMT-B). TMT-A and TMT-B assess a person's ability to sequence and shift perceptual sets, concentration and vigilance, and visuomotor scanning and tracking speed [18], which reflect executive control functioning [18,19].

FDG PET studies

All patients fasted for at least 6 h (blood glucose level <160 mg/dl) and underwent brain dynamic ^{18}FDG PET (Gemini GXL, Philips Medical Systems, Cleveland, OH, USA) scan. Details of the PET study were explained to the patients and they provided written informed consent as established by our Ethics Committee. After intravenous bolus administration of ^{18}FDG (ranging from 185 to 200 MBq) [20], a dynamic list-mode acquisition protocol was started, lasting 60 min. Data were corrected

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. The baseline characteristics of patients and risk factors associated with WMIL patients and case control group.

Variable	WMIL (n=18)	Case control (n=18)	*P*
Female, n (%)	7 (38.9)	8 (44.4)	0.459
Age, years, mean ±SD	68.7±5.1	69.2±5.5	0.743
Education, years, mean ±SD	5.9±5.4	5.3±6.3	0.152
Current smoking, n(%)	8 (44.4)	9 (50.0)	0.657
Alcohol habits, n(%)	5 (27.8)	6 (33.3)	0.594
Chronic hypertension, n(%)	9 (50.0)	8 (44.4)	0.692
Diabetes mellitus, n(%)	11 (61.1)	11 (55.6)	0.513
Cardiopathy, n(%)	4 (22.2)	5 (27.8)	0.391
Dyslipidemia, n(%)	13 (66.7)	12 (72.2)	0.33

* *P*<0.05. Data are expressed as: mean ±SD and no. (percent). WMIL – white matter ischemic lesion.

Table 2. Neuropsychological performance.

Variable	Case group	Case control group	*P*
TMT-A	104.5±10.8	89.6±13.7	<0.001*
TMT-B	203.0±16.9	181.6±14.0	<0.001*
MoCA	22.8±2.1	24.3±2.4	0.0431*
MMSE	26.0±2.3	26.8±3.1	0.0722

* *P*<0.05. Data are expressed as: mean ±SD and no. (percent). TMT – trail making test; MoCA – Montreal Cognitive Assessment; MMSE – Mini-Mental State Examination.

for random events, dead time and attenuation; images were reconstructed using an iterative method of line of response (3-D row action maximum likelihood algorithm LOR) implemented by Philips. Images were visualized and analyzed using a dedicated software package (PMOD, University of Zurich, Switzerland [15,21]) in coronal, sagittal, and transverse views.

Data analysis

All statistical analyses were conducted using SPSS software, version 16.0 (IBM, Armonk, NY, USA). Data are expressed as means ± standard deviation (x±s). First, an analysis to check whether cases and controls were matched on the main socio-demographic variables (sex distribution, age, and educational level) was performed. Group differences in demographic variables, MoCA scores, and MMSE scores were examined using one-way analysis of variance (ANOVA) or chi-square analysis. The Pearson correlation was used to analyze the associations between CMRglu and TMT. Mean differences for each pair of sessions were compared using the least significant difference (LSD) test. Variables were analyzed by univariate and then multivariate logistic regression. All remaining variables were entered in the analysis as binary variables (present/absent). A value of P<0.05 was considered indicative of a statistically significant difference.

Results

This was a case-control study involving 30 WMIL patients and 30 healthy control subjects. No white matter lesions were detected in the control group. The sex, age, and education level were very comparable between the 2 groups. A detailed description of the demographics of the patients included in our study is shown in Table 1. Briefly, the patients in the WMIL group had higher rates of diabetes and blood pressure. However, there were no significant differences in these parameters between the 2 groups. The other cerebrovascular disease risk factors were also similar in the 2 groups.

The MMSE scores were lower for the WMIL group; however, there was no significant difference in MMSE scores between the WMIL group and the control group (Table 2). The results of this study demonstrate the accuracy of MoCA in the diagnosis of WMIL patients' cognitive impairment. When the subjects were grouped by decade of age, a statistical difference was observed between MMSE score and MoCA score in the 8th decade (70–79 years old) (Table 3).

The most common impairments in 30 WMIL patients were executive dysfunction (n=13; 43.3%), followed by memory (n=11;

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 3. Clinical measures grouped by decade.

Decade (years)	N(60)	Age (years)	MMSE score; rrange	MoCA score; range	*P*
7th (60s)	36	64.6±5.9	26.9±2.3;(24–29)	23.5±2.1; (21–26)	0.0516
8th (70s)	24	75.1±6.5	26.1±1.8; (24–28)	23.0±1.6; (20–25)	0.0412*
Mean	–	68.1±7.8	26.6±2.6; (24–29)	23.3±2.3; (20–26)	0.0475*

* $P<0.05$. Data are expressed as: mean ±SD. MMSE – Mini-Mental State Examination; MoCA – Montreal Cognitive Assessment.

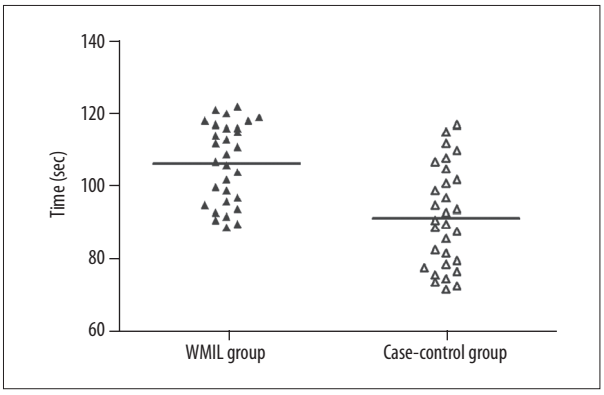

Figure 1. The mean time of TMT-A in the two groups. The results indicated that there is a statistically significant difference in TMT-A.

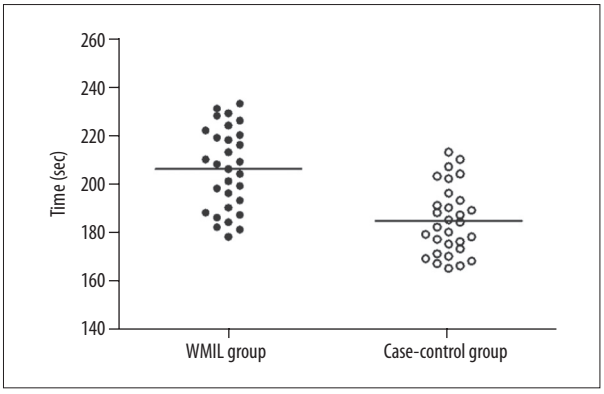

Figure 2. The mean time of TMT-B in the two groups. The results indicated that there is a statistically significant difference in TMT-B.

36.7%) and attention (n=9; 30.0%) impairments. Orientation to time and place impairments (n=2; 6.7%) as well as visuospatial functional impairments (n=3; 10.0%) were the least common. Of the 13 WMIL patients who showed executive dysfunction, most exhibited impairment in cube copying (n=7; 46.2%) or trail making (n=9; 69.2%), and 3 subjects (23.1%) displayed impairments in both.

The mean time of TMT-A was 104.5±10.82 s in the case group and 89.6±13.65 s in the control group. For TMT-B, the mean time

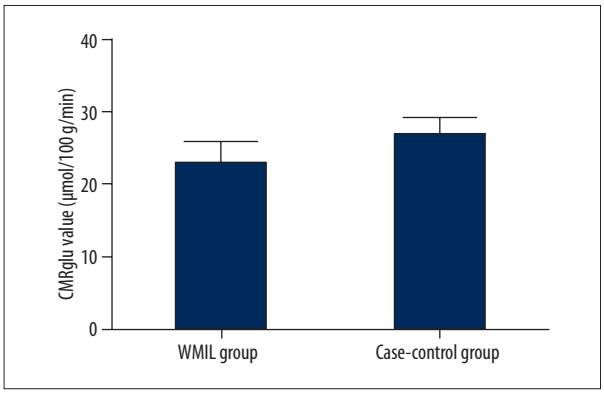

Figure 3. Mean CMRglu in total gray matter in WMIL group *vs.* case-control group.

was 203.0±16.87 s and 181.6±14.02 s, respectively (Table 2). The results show statistically significant differences both in TMT-A and TMT-B (Figures 1 and 2). The case group was slower than the control group.

No significant differences were observed for any of the brain regions delineated between left and right CMRglu values (data not shown). Compared with the controls, the CMRglu values of gray matter were decreased in the WMIL group (Figure 3). Reductions of CMRglu in parietal lobe, frontal lobe, and white matter centrum semiovale were observed to different degrees in the WMIL groups according to the modified Fazekas scale. Figures 4 and 5 show the mean of CMRglu in the right frontal lobe and right temporal lobe in different degrees of WMIL patients according to the Fazekas scale. However, there were no significant differences among the 3 levels of WMIL groups in parietal lobe or occipital lobe (Table.4). No recent publications were available for comparison of these separate parameters in China. Furthermore, our study shows the negative correlation between TMT time and the right frontal lobe CMRglu value (Figure 6).

Discussion

To the best of our knowledge, this is the first PET research in China to focus on factors that affect cognitive impairment. We have shown here that the MoCA, but not the MMSE, has

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

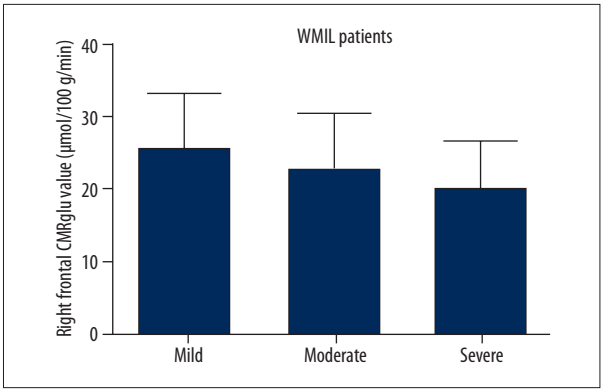

Figure 4. Mean CMRglu in right fronatl lobe in different degree of WMIL patients according to the Fazekas scale.

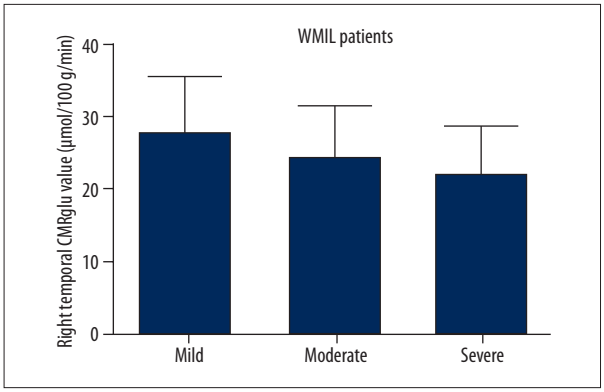

Figure 5. Mean CMRglu in right temporal lobe in different degree of WMIL patients according to the Fazekas scale.

Table 4. Comparison of CMRglu in different degree of WMIL.

Brain region (left)	Mild (n=9)	Moderate (n=15)	Severe (n=6)	*F*	*P*
Frontal	25.3±7.8	22.4±8.1	19.8±6.5	23.5	<0.001*
Temporal	27.4±8.3	24.1±7.4	21.6±7.1	25.2	<0.001*
Parietal	27.9±6.5	26.5±6.9	25.8±7.3	9.2	0.552
Occipital	23.9±7.2	22.5±6.7	22.3±6.5	3.2	0.697
White matter centrum semiovale	13.0±3.6	10.6±4.4	9.1±3.5	11.4	0.047*

Data are expressed as: mean ±SD and no. (percent). Units: μmol 100 $g^{-1}min^{-1}$ (mean ±SD). * Statistically significant differences between sessions (P<0.05).

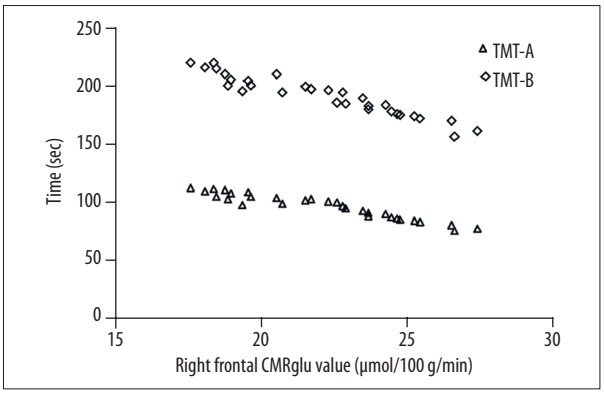

Figure 6. Scatterplots for TMT and CMRglu in frontal for patients with WMIL.

adequate psychometric properties as a screening instrument for the detection of mild cognitive impairment in WMIL disease.

Naming and orientation were preserved even in patients with low MoCA scores. In contrast, cube copying (1 point), clock drawing (3 points), and trail making (1 point) scores decreased remarkably even in high MoCA score patients. We observed differences between the MoCA and MMSE subtests that measured similar abilities. For instance, the MoCA includes a 5-word delayed recall test, whereas the MMSE provides a 3-word delayed recall test; even for patients with high MoCA scores, 5-word recall was difficult according to the MoCA, whereas 3-word recall according to the MMSE was relatively preserved [22]. In addition, the MoCA includes a subtest in which 2 sentences are repeated, whereas the MMSE includes a subtest in which a single sentence is repeated. Furthermore, the length and complexity of the sentences are greater in the MoCA [23]. These results suggest that MMSE might lack specificity for cognitive impairment screening.

Previous ^{18}FDG PET methodology studies had demonstrated hypometabolism in the cerebral hemisphere of ischemic stroke patients [24]. This is in line with the present data, which shows decreased CMRglu in patients with WMIL as compared with controls. Ours is the first study using ^{18}FDG PET methodology in WMIL patients in China. In WMIL patients (n=30), total gray matter CMRglu was lower than in controls. The strong correlation between CMRglu and cognitive function in ischemic lesion patients has previously been demonstrated [16,25]. This study found that lower CMRGlu predicted executive function impairment (Figure 6), which is in line with the earlier reported results. As in experimental focal WMIL, where metabolism was found to be related to cellular loss, these metabolic studies using PET assessed the condition of

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

the WMIL tissue and its propensity for functional deterioration [25]. On the other hand, the results stressed the importance of the functional capacity of the whole brain in coping with a focal defect. The data suggest that WMIL is a chronic condition leading to ischemic cellular losses in the brain [26,27]. These findings point to a possible pathomechanism of WMIL and a potential role for CMRglu as a biomarker for predicting the severity of WMIL.

Our study had several limitations. First, determination of the specificity and sensitivity of the MoCA for cognitive impairment in our population could not be made because formal neuropsychological testing was not performed. Second, undergoing the battery of cognitive assessments in addition to the MMSE and MoCA likely caused fatigue in our subjects, which may have increased the probability of error, although to compensate we offered a 5- to10-min rest in the middle of the assessment sessions or spread assessments over 2 consecutive days. Finally, our sample size was not sufficiently large, limiting statistical power.

Conclusions

MoCA appears to be a more sensitive screening tool than the commonly used MMSE for detecting cognitive impairment in patients with WMIL. Glucose metabolism measured with positron emission tomography was decreased in patients with white matter ischemic lesion. A significant negative correlation was found between executive function and CMRglu in the frontal lobe. These findings suggest a possible pathomechanism of WMIL and a potential role for CMRglu as a biomarker for predicting the severity of WMIL. However, the influence of glucose metabolism on cognitive impairment resulting from white matter ischemic lesion is variable and merits further research.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References:

1. Henninger N, Khan MA, Zhang J et al: Leukoaraiosis predicts cortical infarct volume after distal middle cerebral artery occlusion. Stroke, 2014; 45: 689–95
2. Zimny A, Bladowska J, Neska M et al: Quantitative MR evaluation of atrophy, as well as perfusion and diffusion alterations within hippocampi in patients with Alzheimer's disease and mild cognitive impairment. Med Sci Monit, 2013; 19: 86–94
3. Henon H, Vroylandt P, Durieu I et al: Leukoaraiosis more than dementia is a predictor of stroke recurrence. Stroke, 2003; 34: 2935–40
4. Jaillard A, Naegele B, Trabucco-Miguel S et al: Hidden dysfunctioning in subacute stroke. Stroke, 2009; 40: 2473–79
5. Chutinet A, Rost NS: White matter disease as a biomarker for long-term cerebrovascular disease and dementia. Curr Treat Options Cardiovasc Med, 2014; 16: 292
6. Miki Y, Sakamoto S: Age-related white matter lesions (leukoaraiosis): an update. Brain Nerve, 2013; 65: 789–99
7. Macfarlane MD, Looi JC, Walterfang M et al: Executive dysfunction correlates with caudate nucleus atrophy in patients with white matter changes on MRI: a subset of LADIS. Psychiatry Res, 2013; 214: 16–23
8. Black S, Gao F, Bilbao J: Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. Stroke, 2009; 40: S48–52
9. Kataev GV, Korotkov AD, Kireev MV, Medvedev SV: Factor structure of regional CBF and CMRglu values as a tool for the study of default mode of the brain. Fiziol Cheloveka, 2013; 39: 60–66
10. Huisman MC, van Golen LW, Hoetjes NJ et al: Cerebral blood flow and glucose metabolism in healthy volunteers measured using a high-resolution PET scanner. EJNMMI Res, 2012; 2: 63
11. Bohnen NI, Minoshima S: FDG-PET and molecular brain imaging in the movement disorders clinic. Neurology, 2012; 79: 1306–7
12. Granov AM, Tiutin LA, Stanzhevskii AA: The application of nuclear medicine imaging in neurology, neurosurgery and psychiatry. Vestn Ross Akad Med Nauk, 2012: 13–18
13. Schmidt R, Berghold A, Jokinen H et al: White matter lesion progression in LADIS: frequency, clinical effects, and sample size calculations. Stroke, 2012; 43: 2643–47
14. Calabro RS, Gervasi G, Baglieri A et al: Is high oral dose L-arginine intake effective in leukoaraiosis? Preliminary data, study protocol and expert's opinion. Curr Aging Sci, 2013; 6: 170–77
15. Dubois A, Herard AS, Flandin G et al: Quantitative validation of voxel-wise statistical analyses of autoradiographic rat brain volumes: application to unilateral visual stimulation. Neuroimage, 2008; 40: 482–94
16. Benisty S, Gouw AA, Porcher R et al: Location of lacunar infarcts correlates with cognition in a sample of non-disabled subjects with age-related white-matter changes: the LADIS study. J Neurol Neurosurg Psychiatry, 2009; 80: 478–83
17. Yuan JL, Wang SK, Peng P et al: Characteristics of cognitive impairment in patients with leukoaraiosis. Zhonghua Yi Xue Za Zhi, 2012; 92: 147–51
18. Podemski R, Pokryszko-Dragan A, Zagrajek M et al: Mild cognitive impairment and event-related potentials in patients with cerebral atrophy and leukoaraiosis. Neurol Sci, 2008; 29: 411–16
19. Sudo FK, Alves CE, Alves GS et al: White matter hyperintensities, executive function and global cognitive performance in vascular mild cognitive impairment. Arq Neuropsiquiatr, 2013; 71: 431–36
20. Rissanen E, Virta JR, Paavilainen T et al: Adenosine A2A receptors in secondary progressive multiple sclerosis: a [(11)C]TMSX brain PET study. J Cereb Blood Flow Metab, 2013; 33: 1394–401
21. Cook EH Jr, Metz J, Leventhal BL et al: Fluoxetine effects on cerebral glucose metabolism. Neuroreport, 1994; 5: 1745–48
22. Osafune M, Deguchi K, Abe K: Ideal combination of dementia screening tests. Nihon Ronen Igakkai Zasshi, 2014; 51: 178–83
23. Wong GK, Lam SW, Wong A et al: MoCA-assessed cognitive function and excellent outcome after aneurysmal subarachnoid hemorrhage at 1 year. Eur J Neurol, 2014; 21: 725–30
24. Nariai T, Ohno K, Akimoto H et al: Cerebral blood flow, vascular response and metabolism in patients with MELAS syndrome – xenon CT and PET study. Keio J Med, 2000; 49(Suppl.1): A68–70
25. Kitamura S, Kato A, Yamamoto YL et al: Cerebral blood flow, cerebral oxygen metabolism, cerebral glucose metabolism, and tissue pH in human acute cerebral infarction using positron emission tomography. No To Shinkei, 1985; 37: 56–64
26. Gasparovic C, Prestopnik J, Thompson J et al: 1H-MR spectroscopy metabolite levels correlate with executive function in vascular cognitive impairment. J Neurol Neurosurg Psychiatry, 2013; 84: 715–21
27. Steinbrich W, Friedmann G, Pawlik G et al: MR of ischemic brain diseases. A comparison with CT, PET (18-fluorodeoxyglucose) and angiographic results. Rofo, 1986; 145: 173–81

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]