NUCLEAR MEDICINE IMAGING IN DEMENTIA

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In this work the authors share their opinion on the role of nuclear medicine imaging in the diagnosis and differential diagnosis of dementias. Perfusion single–photon emission computed tomography using ^{99m}Tc-exametazim and ^{18}F-fluorodeoxyglucose positron emission tomography are highly sensitive and specific; they are recommended for a wide range of clinical applications. The efficacy of amyloid imaging in Alzheimer's is still a matter of discussion, because amyloid accumulation is also typical in patients with other dementias. Dopamine transporter imaging using ^{123}I-ioflupane is a very reliable diagnostic tool for Parkinson's disease and Lewy body dementia, and can help to adjust treatment strategies. Further evolution of nuclear medicine methods will most likely include the development of new radionuclide tracers for such targets as microglial cells' activation and neurofibrillary tangles.

Keywords: nuclear medicine, SPECT, PET, exametazime, ^{18}F-fluorodeoxyglucose, Alzheimer's disease, Lewy body dementia, frontotemporal lobar degeneration, vascular dementia, dopamine transporters, amyloid imaging

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ВОЗМОЖНОСТИ ЯДЕРНОЙ МЕДИЦИНЫ В ДИАГНОСТИКЕ ДЕМЕНЦИЙ

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В работе представлено мнение о применимости различных методов ядерной медицины для диагностики, в том числе дифференциальной, различных деменций. Перфузионная однофотонная эмиссионная компьютерная томография с эксаметазимом и позитронно-эмиссионная томография с ^{18}F-фтордезоксиглюкозой высокочувствительны и высокоспецифичны и рекомендуются для широкого применения в клинической практике. Эффективность визуализации распределения амилоида при выявлении болезни Альцгеймера остается под сомнением, так как накопление амилоида характерно для пациентов с другими деменциями. Визуализация распределения переносчиков дофамина с ^{123}I-иофлупаном крайне эффективна в диагностике болезни Паркинсона и деменции с тельцами Леви: ее результаты могут обусловливать коррекцию тактики лечения. Дальнейшее развитие методов, скорее всего, будет заключаться в разработке новых радионуклидных маркеров к таким мишеням, как клетки микроглии и нейрофибриллярные клубки.

Ключевые слова: ядерная медицина, ОФЭКТ, ПЭТ, эксаметазим, ^{18}F-фтордезоксиглюкоза, болезнь Альцгеймера, деменция с тельцами Леви, фронтотемпоральная дегенерация, сосудистая деменция, переносчики дофамина, визуализация амилоида

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Improvements in life expectancy in the western world are concomitant with increasing prevalence of age-associated diseases, among which dementias amount to 1.5 %. Of all dementia cases, 70 % account for Alzheimer's disease (AD) and 2 0% are vascular dementias. In 2010 there were 35 million people living with various dementias worldwide, with the highest disease prevalence registered in Latin America [1].

Single-photon emission computed tomography (SPECT) and positron-emission tomography (PET) are nuclear medicine techniques used to diagnose dementia at early stages. Just like our colleagues from other countries, here in Russia we use a ^{99m}Tc-exametazime, a technetium-based radiopharmaceutical (RP) for SPECT imaging of regional cerebral blood flow (rCBF). For PET, ^{18}F-fluorodeoxyglucose (FDG) is used to evaluate the rate of glucose metabolism. When deciding on the nuclear medicine technique to monitor patients with neurodegenerative diseases, the doctor should bear in mind the patterns of RP distribution in the brain tissue that largely determine diagnosis accuracy and, therefore, help to elaborate a better treatment strategy. Here, we discuss the value of some radionuclide

neuroimaging techniques for the differential diagnosis of dementias and treatment monitoring and talk about further advances in this area of research.

Clinical efficacy of perfusion SPECT with ^{99m}Tc-exametazime

We believe that perfusion SPECT with ^{99m}Tc-exametazime is one of the most effective techniques used to diagnose neurodegenerative diseases. It allows diagnosing and differentiating between dementias due to various patterns of RP distribution in the brain (fig. 1) [2]. A pattern typical for frontotemporal degeneration (FTD), namely, prevailing hypoperfusion in the frontal cortex, differs significantly from the AD pattern (hypoperfusion in the parietal, prefrontal and posterior temporal cortices) [3]. SPECT is the least effective for differentiating AD from dementia with Lewy bodies (DLB), because imaging patterns of these two disorders are very similar. Dougall et al. [4] report 71.5 % sensitivity and 78.2 % specificity of SPECT when differentiating between AD and FTD; with AD and vascular dementia, the corresponding figures were 71.3 and 75.9 %. When diagnosing AD by comparing patterns of RP distribution in patients and healthy individuals, sensitivity and specificity were 66.0 and 79.0 %, respectively. Yeo et al. [5] provided slightly different statistics: pooled sensitivity and specificity of the method in the differential diagnosis of AD and FTP were 79.7 and 79.9 %, respectively; for AD and vascular dementia the figures were 70.2 and 76.2 %, respectively; when comparing patients with AD and healthy individuals, the figures were 76.1 and 85.4 %, respectively.

The potential of perfusion SPECT as a monitoring tool in the treatment of neurodegenerative disorders has not been studied properly. Efimova et al. [6] demonstrated that brain perfusion and cognitive function improve in the course of antihypertensive therapy by comparing screening results before treatment and six months after it. Murashko [7] studied brain perfusion in patients with hypertonic encephalopathy and demonstrated that therapy with cavinton improved brain perfusion. However, the study sample was too small, and there was no control group. Another important observation was made by Nobili et al. [8], who performed repeat brain perfusion SPECT scans on patients with AD after starting therapy with acetylcholinesterase inhibitors. They showed that if cognitive function was intact, brain perfusion pattern did not change significantly, while in patients with deteriorated cognitive function, who were undergoing treatment, rCBF was reduced. We believe that perfusion SPECT can be a promising tool in the assessment of medication efficacy and prediction of the disease outcome. However, this method still requires further longitudinal studies.

In Russia, perfusion SPECT is not included into the state-approved standard of medical care. Besides, it is quite expensive, therefore, is not used widely. We think that professional medical community should call for the inclusion of this method into the standard of the specialized medical care for patients with Alzheimer's disease and other dementias, given that the equipment necessary for scanning procedures is available in most regional centers.

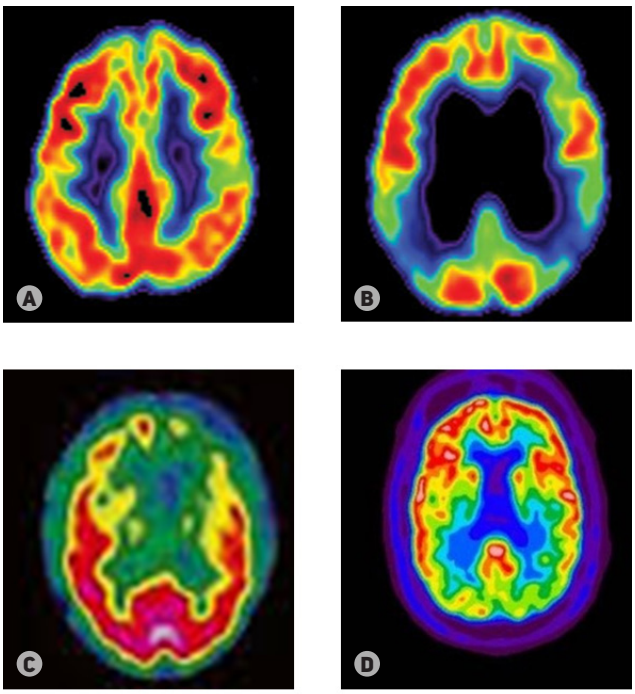

Fig. 1. Brain perfusion SPECT with 99mTc-exametazime, axial sections. **(A)** Intact brain perfusion. **(B)** Perfusion pattern typical for Alzheimer's disease (reduced perfusion in the parietal cortex). **(C)** Perfusion pattern typical for frontotemporal degeneration (reduced perfusion in the frontal cortex). **(D)** Perfusion pattern typical for Lewy body dementia and similar to Alzheimer's; reduced perfusion is observed in the occipital cortex (Dierckx et al. [2])

Clinical efficacy of PET with ^{18}F-fluorodeoxyglucose

We believe that PET with ^{18}F- fluorodeoxyglucose can be used for diagnosing neurodegenerative diseases in the same cases as perfusion SPECT, because patterns of glucose hypometabolism and hypoperfusion are similar: glucose utilization and brain regional perfusion are linked [9]. Both hypoperfusion regions detected by perfusion SPECT with ^{99m}Tc-exametazime and hypometabolism regions found on PET with ^{18}F-FDG reflect structural changes in the brain [10]. PET has a better resolution and ^{18}F-FDG is a more stable radionuclide tracer than ^{99m}Tc-exametazime, which makes this method highly accurate. Davison et al. [11] compared PET with 18F-FDG and perfusion SPECT with ^{99m}Tc-exametazime and found that SPECT sensitivity and specificity were 85.0 and 87.0 %, respectively, while PET sensitivity and specificity were 99.0 and 93.0 %, respectively. However, the authors note that the number of works confirming their findings is low and emphasize the necessity of direct prospective comparative studies in this area of research.

We would like to draw the reader's attention to the work by Kato et al. [12] in which reduced perfusion in inferior parietal lobe, precuneus and posterior cingulate gyrus is described as a predictor of mild cognitive impairment evolution into Alzheimer's disease, in addition to the already known patterns of reduced glucose uptake.

We believe that PET scanning should be used to differentiate between dementias only when other methods have failed and under the condition that scan results will influence the treatment strategy. Specifically, PET with ^{18}F-FDG can be used to support AD diagnosis based on the results of neuropsychological testing, if CT or MRI showed no changes in the brain matter and SPECT findings are ambiguous.

PET in amyloid imaging

For brain amyloid imaging, ^{11}C-Pittsburgh compound B is used. Its clinical application was first described in 2004 [13]. Due to the short half-life of ^{11}C, ^{18}F-based RPs were developed,

including florbetapir, florbetaben and flutemetamol (all approved by American Food and Drug Administration).

We believe that clinical importance of scanning that makes use of RPs exhibiting affinity to amyloids is questionable. This method is very cost-ineffective and can not be included into standard screening procedures. We do not recommend it for the differential diagnosis of dementias, as amyloid plaques can be visualized in patients who do not have AD or suffer from other dementias. In about 20 % of cases, amyloid accumulation is observed in patients with clinically verified FTD, which can be explained by the similarity of AD and FTD symptoms or by concomitant AD and FTD pathologies [14]. About 89 % of patients with DLB accumulate RPs with affinity to amyloids. Still, it is not a false positive result, but rather a reflection of a pathophysiological process [2].

We do not recommend amyloid imaging for the assessment of dementia severity and therapy progress, because amyloid deposition is markedly slowed after the onset of mild cognitive impairments. From that moment, amyloid imaging becomes ineffective, as amyloid accumulation surrenders its leading role in cognitive function deterioration to the structural changes in the brain. Perfusion SPECT or PET with ^{18}F-FDG describe the course of the disease better.

Dopamine transporter imaging

The reduced number of dopamine transporters in the putamen is a hallmark of Parkinson's disease and Lewy body dementia. Visualization of dopamine transporter distribution in patients is performed using ^{123}I-ioflupan. It has a high affinity to dopamine transporters and binds to them in the striate bodies. SPECT scanning can evaluate their number reduction (fig. 2) [15].

This method can be recommended for clinical use, as it is a highly effective diagnostic tool: with DLB, its sensitivity is over 70.0 % and specificity is over 90.0 % [16]. We believe that scan results can be a basis for the adjustments in the treatment plan. A randomized study conducted by Walker et al. [17] confirmed that if the scan result is positive (suggesting DLB), doctors make necessary corrections to the diagnosis and treatment strategy. Wide clinical application of this method is restricted by ^{123}I-ioflupan high price.

CONCLUSIONS

Radionuclide techniques are effective ancillary tools in the diagnosis and differential diagnosis of dementias, especially at early stages of the disease when morphological changes in the brain have not yet set in. Available in Russia, perfusion SPECT and PET are highly sensitive and specific. They are also very effective as a monitoring tool for assessing the progress of the neurodegenerative disease when combined with longitudinal studies, but their application is restricted by a high price of radionuclide tracers.

We believe that dopamine transporter imaging is highly effective and can be used to diagnose Lewy body dementia and parkinsonian syndromes along with the development of novel RPs. At the same time, amyloid imaging is the least effective in the differential diagnosis of various dementias due to the high cost of RPs and difficult interpretation of the results. We recommend this scanning procedure should be introduced in a few federal medical centers for studying complicated cases of dementias at early stages and conducting scientific research; new radionuclide tracers should be developed in cyclotron radiochemistry labs in parallel.

Further evolution of nuclear medicine techniques for the diagnosis of neurodegenerative diseases will depend on the development of more specific radionuclide tracers, including those that detect microglial cells activation (^{11}C-PK11195) [18]. Another potential target for diagnostic imaging in patients with dementias is neurofibrillary tangles. At the moment, new RPs are being developed for their targeting. However, one of such radionuclide tracers, ^{18}F-FDDNP, is still less effective than Pittsburgh compound B and ^{18}F-FDG in predicting the disease progress [19].

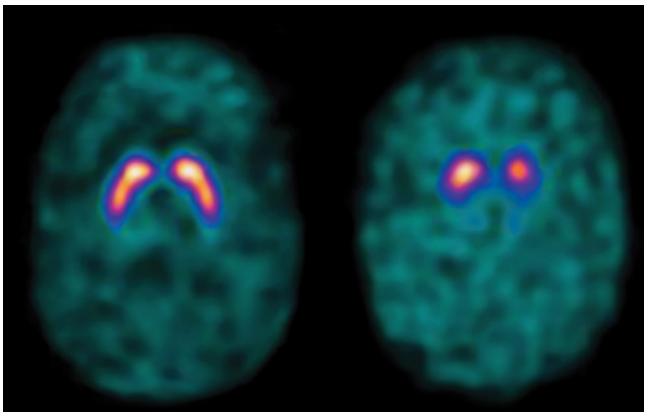

Fig. 2. SPECT with 123I-ioflupan shows distribution of dopamine transporters. The picture shows axial sections at the striatal level. Left: a section obtained from a healthy volunteer. Right: a section obtained from a patient with Parkinson's disease (Hauser et al. [15])

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