Imaging Methods Applicable in the Diagnostics of Alzheimers Disease,Considering the Involvement of Insulin Resistance with Clinical Pharmacological Point

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Abstract

The fact that Alzheimer's disease is related to impaired insulin signaling and glucose metabolism in the brain is widely known, and for this reason it has been said that Alzheimer's disease is a special form of diabetes and it is called type 3 diabetes.

Materials and methods:

This experimental study was conducted in 1402 at the University of Medical Sciences. A total of 60 people were diagnosed with Alzheimer's disease using imaging methods, also people were examined for diabetes and diabetic people were included in this research. The effect of insulin resistance on Alzheimer's disease was investigated using imaging methods. The data of the present study were collected and one-way ANOVA and (Tukey's post hoc test) were used to analyze the data. Also, a significance level of $P<0.05$ was considered.

Conclusion:

The pathological symptoms of Alzheimer's disease are the appearance of intracellular phosphorylated tau proteins and extracellular beta amyloid plaques, which are created by beta and gamma secretase enzymes from the amyloid precursor protein. Amyloid beta and phosphorylated tau proteins cause local poisoning of neurons and eventually lead to the death of neurons and the occurrence of Alzheimer's disease. Therefore, early diagnosis of Alzheimer's disease plays an important role in reducing its complications.

Keywords: imaging methods_ Alzheimer's_insulin resistance.

Introduction

Insulin in the brain regulates many key processes such as food intake, homeostasis, energy, reproductive endocrinology, sympathetic activities, peripheral insulin action, even learning, memory, neuronal proliferation, apoptosis, transmission and synaptic transmission. In this situation, any disorder in insulin metabolism, in , the brain may leave adverse effects (1). There is a lot of evidence that shows that insulin and insulin signaling are important for the survival of neurons. With the studies conducted on the brains of Alzheimer's patients, it has been shown that the expression of the insulin receptor is reduced in them(2). Currently, it is widely

recognized that Alzheimer's disease is related to impaired insulin signaling and glucose metabolism in the brain, and for this reason, it has been suggested that Alzheimer's disease is a special form of diabetes and called type 3 diabetes(3). have given it High blood insulin (similar to what happens in type 2 diabetes) is one of the risk factors of Alzheimer's disease. The pathological signs of Alzheimer's disease are the appearance of intracellular phosphorylated tau proteins and extracellular beta amyloid plaques, which are formed by beta and gamma secretase enzymes from the amyloid precursor protein(4). Amyloid-beta and phosphorylated tau proteins cause local poisoning of neurons and ultimately lead to the death of neurons and the occurrence of Alzheimer's disease. Beta amyloid can stimulate the removal of insulin receptors from the membrane of neurons, and this leads to more resistance to insulin in neurons (5). Undoubtedly, memory loss is one of the main symptoms of Alzheimer's disease, but there are other symptoms that are an alarm for the onset of this disease. Sometimes, Alzheimer's disease may show itself by forgetting voluntary movements, according to experts, about 42% of people with Alzheimer's suffer from anxiety in addition to memory disorders. Although memory disorders are the most characteristic symptom of Alzheimer's disease, in 10% of cases it does not show itself as the first symptom(6). Alzheimer's disease (AD) is the most common type of dementia in the elderly. AD is a progressive disease that destroys neurons, characterized by memory dysfunction and cognitive loss, and the reason for this is a neurocircuitry disorder(7). Mild cognitive impairment (MCI) is an intermediate stage before dementia, and MCI people have a rate of -10 15% progress to AD each year. While healthy people develop dementia at a rate of 1-2% per year with age, there is no definitive diagnosis and treatment for this disease, and there are only methods to slow the progression of the disease(8). Early diagnosis of this disease is very important in slowing down the progression of the disease. So far, there have been various methods to chec Reducing Cardiac brain function. The method that is used today more than others to diagnose the brain areas and the connections in it is functional magnetic resonance imaging (MRI)(9). In addition to the MRI method, other methods such as electroencephalography (EEG), magnetoencephalography (MEG) and positron emission tomography (PET) are also used to determine the location of neural activity and the communication of areas in the brain. Among the mentioned methods, functional magnetic resonance imaging as a non-invasive tool with high spatial resolution has attracted the attention of many researchers(10). EEG and MEG signals directly show the brain activity, but in MRI and PET methods, the image obtained It is the result of changing an intermediary factor(11). MRI method is a non-invasive imaging method that has a good spatial resolution and has been proven to be sensitive to brain changes in the early stages of the disease, considering the problems of the task-based MRI method, especially for studying the brain of sick people(12). Resting state MRI (rs-MRI)) is a suitable method to understand the changes in brain function due to disease, on the other hand, MRI only examines the brain function without considering the brain structure(13). In addition to the rs-fMRI method, using the sMRI method, the structure of the brain should also be investigated with the aim of predicting Alzheimer's disease. Spontaneous brain activities measured by rs-fMRI are summarized by a number of resting state distinct networks (RSNS) that have similar temporal characteristics(14). In recent years, the prediction of Alzheimer's disease has attracted the attention of many scientists, and various methods based on MRI images have been used. In MRI images, structural connections refer to a physical or synaptic network that a group of neurons or nerve elements create with each other(15). Graph theory is a suitable tool to investigate the organization of brain network topology based on rs-fMRI data. In addition to the strength of the connection between the regions, the study of the brain network can also determine the direction of the connections between the regions(16). Graph theory is actually a method that analyzes the networks in the brain and examines them, and it has many applications in identifying various diseases. In recent studies, it was shown that the combination of graph theory and machine learning methods based on functional images leads to the accurate separation of Alzheimer's patients(17). The use of structural images in the diagnosis of Alzheimer's disease has been of interest to researchers from the past to the present, but the use of these images The limitation of extractable features and the subsequent decrease in predictive accuracy have been a problem for researchers(18). By using MRI images, it is possible to extract the most effective features from these images and achieve an acceptable percentage of accuracy(19). In past studies, it has been shown that the integration or combination of two or more types of imaging leads to an increase in quality or efficiency(20). Mr. Simon and his colleagues succeeded in identifying areas of the brain that are effective in predicting Alzheimer's disease by using the cortical thickness pattern. In this article, using data extracted from Mr. Wells's article, and with the aim of improving the accuracy of this article, they combined MRI data with other effective parameters in Alzheimer's disease(21). According to the review of articles in the field of predicting Alzheimer's disease, no study has been conducted to predict Alzheimer's disease based on fMRI-rs. fMRI-rs imaging is a powerful tool for

mapping and investigating the function of different brain networks(22). MRS imaging is a non-invasive imaging technique that is used to study metabolic changes in the brain, stroke, seizure disorders, Alzheimer's disease, depression, and metabolic changes in other parts of the body such as muscles. In this imaging method, various metabolic information can be obtained at the same time, and unlike mass spectroscopy or other common methods, there is no need to isolate(23). The main difference between MRI and MRS is their use of the MR signal frequency to encode information. In conventional MR imaging methods, the signal generated by the hydrogen atom nucleus is obtained from a very small voxel characterized by spatial changes in frequency and phase(24). By applying the gradient, the magnetic field changes depending on the location, and as a result, the oscillation frequency in each location is determined according to the position in the magnetic field, which ultimately creates these frequency fluctuations of spatial images(25). Since the signal-to-noise ratio in MRS is lower than that of MRI, the selected volume is considered larger for performing MRS (26). According to the mentioned materials and the benefits of diagnosing Alzheimer's disease, the present study was conducted with the aim of The evaluation of the imaging methods that can be used in the diagnosis of Alzheimer's disease was carried out according to the involvement of insulin resistance with the clinical pharmacological point.

analysis method

This experimental study in 1402 investigated insulin resistance and Alzheimer's patients. A total of 60 people were diagnosed with Alzheimer's using imaging methods in Tehran neurology hospitals, including Erfan, Khatam al-Nabiya, Dr. Samii, Ibn Sina, and Alzheimer's and MS patients who visited private clinics in Tehran. Also, people were examined for diabetes and diabetic people were included in this research. The effect of insulin resistance on Alzheimer's disease was investigated using imaging methods. The data of the present study were collected and one-way analysis of variance and (Tukey's post hoc test) were used to analyze the data. Also, a significance level of $P<0.05$ was considered.

Methods	Principal Advantages	Principal Disadvantages
CT	short examination time; less critical contraindication criteria	X-ray exposure; contrast agents may worsen kidney function; poorer definition of critical brain structures (hippocampus, brain stem)
MR methods	no radiation exposure; less expensive examination; widespread availability; wide range of examinations; (standardly) no contrast agents	relatively poor pathological specificity; contraindication criteria (presence of magnetic non-compatible medical devices or foreign bodies); uncomfortable with noise and limited size of MR-gantry
MRI	high-resolution morphology	insensitive to small amount of calcification and bone fracture
MR-volumetry	sensitive tissue volume changes	several non-standardized softwares
fMRI	disrupted brain functions	challenging tasks for attention
MRS	non-invasive detection of metabolic changes	robustness; difficult absolute quantification; non-unambiguous predictive or distinguishable biomarkers
diffusion MRI (DWI, DTI)	demyelinated axons; damaged nerve tracks; 3D visualization of neural pathways	pitfall of mucinous or hemorrhagic lesions; highly motion sensitive
perfusion MRI (ASL, DCE, DSC)	acute inflammation; tissue degradation; ! in the case of ASL no contrast agent	susceptibility artifacts; ! in the case of non-ASL methods (DCE, DSC) contrast agent
PET and SPECT	definitive diagnostics; functional and molecular pathological processes	radiation exposure; more expensive examination; not routine equipment; Tau tracer (Tauvid©) not registered by EMA and thus not commercially available in EU

Discuss

Clinical symptoms of Alzheimer's disease:

Symptoms of Alzheimer's disease include memory loss, personality changes, depression, anxiety and other mental disorders (1). Recent research shows that the combination of information obtained from different biomarkers greatly increases the power of diagnosing cognitive diseases. In fact, different biomarkers produce information that complement each other (2). Researchers have found that using artificial intelligence tools to extract information from brain biomarkers and combine them together can greatly help improve the accuracy of diagnosis or prognosis of cognitive diseases such as Alzheimer's(3). In recent studies, these features are extracted using different feature extraction methods MRI: magnetic resonance imaging, CSF (PET: positron

emission tomography), Bio-extracted, there are a number of features that cause the classification process to deviate and reduce its accuracy. Therefore, the use of feature selection methods can be useful in this field (4) . using communication network analysis methods, the local and topological features of the network are extracted and after building the core matrix of each one, they are integrated with the help of multi-core learning and have reached a new and very accurate method for diagnosing cognitive diseases(17). a new method in the diagnosis of Alzheimer's disease using the random combination method and backward feature selection. In this method, they first extracted features from different areas of the brain, and then using random features and the backward feature selection method, they determined the subsets of features that can bring the most accuracy in the diagnosis of Alzheimer's disease(19). Regarding Alzheimer's disease, so far results and activities have been carried out in the discussion of diagnosis through MRI images such as (11), but the point of all of them is that their accuracy and convergence are variable and relatively low. The main motivation of this research is to provide an intelligent method in The diagnosis of this disease is based on examining the white and gray areas of the brain on MRI images(14).

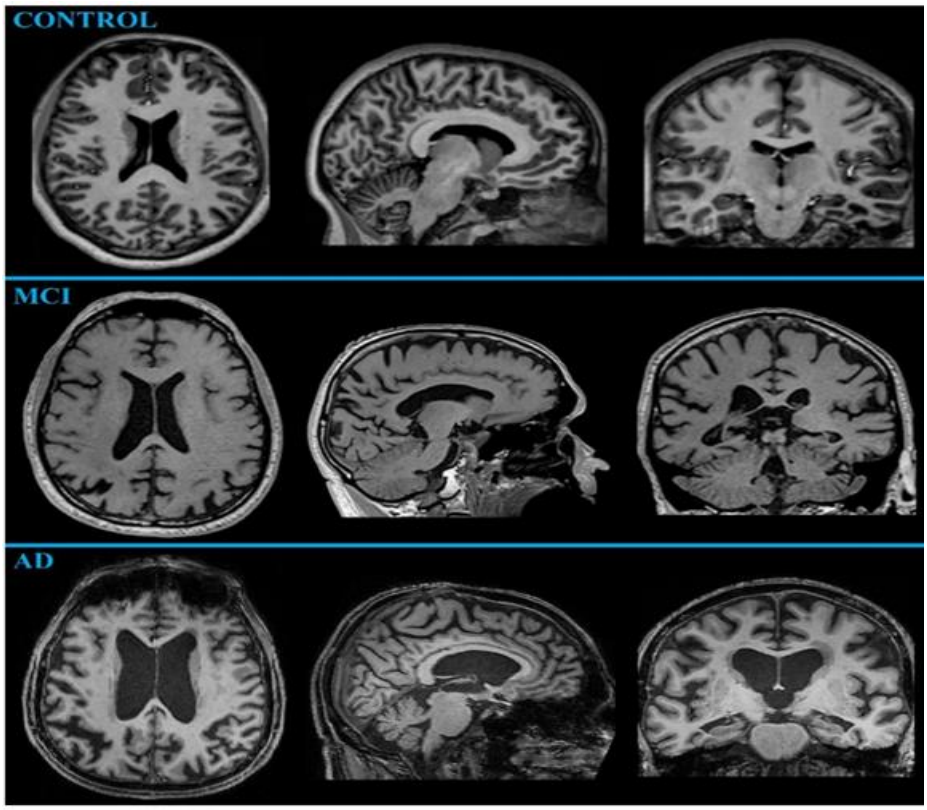

Figure1. Example of MRI (T1-weighted MRI at 3 Tesla MR-scanner), DWI, and DTI (performed on DSI studio software incorporating MATLAB postscripts) neuroimaging of a control subject (50- year-old male) and AD patient (56-year-old female). AD exhibits more restricted diffusion in the tissue, a worse global network density, and lost white matter fiber tracts. Abbreviations: ADC, apparent diffusion coefficient; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; FA, fractional anisotropy(22-60).

Application of MRS in Alzheimer's disease

Alzheimer's disease is a progressive neurological disease whose symptoms are cognitive decline, gradual disruption in daily activities, various neuropsychological symptoms and behavioral disorders. In this disease, MRS shows neurochemical changes caused by increased oxidative stress and changes in fat metabolism with the progression of the disease, as well as an increase in the ml/Cr ratio and a decrease in the NAA/Cr ratio(18) . MRS spectrum can be used to investigate the effect of drugs used in Alzheimer's disease on the reduction of mI level and also the existence of a relationship between this reduction and the improvement of clinical outcome(16). Alzheimer's disease is the most common neurodegenerative disease of the brain in the world, which increases with age(15). This disease is a form of dementia with an unknown

cause. In 95% of cases, the main cause of this disease is the slow destruction of brain cells, which leads to impaired memory, thinking, behavior and finally death(16). The number of people suffering from this disease in 2010 was about 35 million people, if there is no preventive treatment, this number will double every 20 years . There is a lot of evidence that shows that insulin and the insulin signaling mechanism are important for the survival of neurons . Studies have shown a decrease in insulin receptor expression in the brain of people suffering from Alzheimer's disease(17) . These two issues have attracted the attention of many researchers to determine and describe the role that insulin dysfunction can have in the occurrence of Alzheimer's disease. This rapid growth of articles dealing with the relationship between Alzheimer's and insulin has led to the description of Alzheimer's disease as "diabetes of the brain"(18). Currently, it is widely recognized that Alzheimer's disease is associated with impaired insulin signaling and glucose metabolism in the brain. For this reason, it has been suggested that Alzheimer's disease is a special form of diabetes, and for this reason, it has been named type 3 diabetes (12.24.25.26). The pathological signs of Alzheimer's disease are the appearance of intracellular tau phosphorylated proteins and extracellular beta amyloid plaque. Beta amyloids and phosphorylated tau proteins cause local poisoning of neurons, which ultimately leads to the death of neurons and the occurrence of Alzheimer's disease(12.13.14).

Conclusion

Neuroimaging (in particular, the basic methods of radiology and nuclear medicine) remains a fundamental diagnostic step toward identifying AD and monitoring its progression. Furthermore, new technological modalities of neuroimaging combined with modern artificial intelligence and machine learning approaches have further potential to advance the diagnostic and prognostic algorithms in identifying neurodegenerative disorders and monitoring their progression or efficacy of treatment regimens(11). Recent advances in the understanding of AD pathoetiology indicate that AD is not purely a neurodegenerative disease but rather a highly complex metabolic disease affecting not only the central nervous system but also other organs such as the liver and pancreas. Therefore, pathological changes at the level of their functions and structures might be of great importance, mainly because of their involvement in AD pathogenesis during the prodromal phase of the disease(16). Furthermore, disturbed insulin homeostasis and glucose metabolism associated with MCI and AD led to the hypothesis that AD could be an insulinopathy. This has triggered an outburst of research, bridging the molecular pathophysiology of the pancreas, liver, and brain in MCI and AD, which has resulted in the identification of prominent overlaps between, at first sight, very distant disease units,namely AD and DM(18). This new way of looking at AD pathoetiology also makes a reevaluationof the diagnostics, treatment, and preventive strategies for AD an urgent undertakingIn light of the foregoing, it becomes obvious that the use of comprehensive examinations combining above-standard neuroimaging methods with suggestive non-neuronal imaging, of at least the liver and pancreas, may strengthen the diagnostic algorithm in MCI patients, early AD patients, and patients at a higher risk of cognitive impairment due to DM and prediabetes. Moreover, further identification of relevant combinations of radiological and biochemical/molecular markers is much needed to ensure the quality and widespread accessibility of standardized AD diagnostics and monitoring of disease progression(15-62).

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