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# Modern Imaging Methods in the Diagnosis of Neurodegenerative Diseases

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**ABSTRACT**

**Introduction**

Neurodegenerative diseases, such as Alzheimer's, Parkinson's and other forms of dementia, represent a major global health challenge. Early diagnosis and monitoring of disease progression are key to effective management of these conditions. Advanced brain imaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission tomography (SPECT) and functional magnetic resonance imaging (fMRI), play a key role in the diagnosis and monitoring of neurodegenerative diseases. This article outlines the various imaging methods, their application in the context of major neurodegenerative diseases, as well as the advantages and limitations of each. In addition, the prospects for the development of these technologies, including the use of artificial intelligence and new biomarkers in diagnosis, are also discussed.

**Aim of the Study**

To analyze the role of modern imaging methods in the diagnosis and monitoring of neurodegenerative diseases such as Alzheimer’s and Parkinson’s disease.

**Materials and Methods**

A literature review was conducted using PubMed, Oxford Academic, and ScienceDirect databases. The focus was on the application of MRI, PET, SPECT, and fMRI in assessing structural and functional brain changes, their diagnostic precision, and their use in clinical practice.

**Keywords:** neurodegenerative diseases, imaging, cortical atrophy, Alzheimer's disease

**Neurodegenerative diseases - definition and clinical significance.**

Neurodegenerative diseases are a group of conditions in which there is progressive and irreversible damage to the cells of the nervous system, mainly neurons, and impairment of their function. The characteristic feature of these diseases is the degeneration of specific brain structures or areas of the nervous system, which leads to pronounced neurological and cognitive deficits.

The process of developing neurodegenerative diseases begins long before the first clinical symptoms appear and is often asymptomatic for many years. Symptoms become noticeable only when a significant number of neurons are damaged or when degeneration involves key areas of the central nervous system [1].

Examples of the most common neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) or Huntington's chorea.

The clinical significance of these conditions stems from their impact on the quality of life of patients and caregivers, as well as the high social and economic costs associated with health care and long-term treatment.

Neurodegenerative diseases are a major cause of disability in old age and are a growing challenge in aging societies.

Due to the lack of effective causal therapies, early recognition and monitoring of progression plays key role in the fight against these conditions, which allows for more effective implementation of therapeutic strategies and improved quality of life for patients.

The importance of imaging in the diagnosis and monitoring of neurodegenerative diseases

Medical imaging is one of the cornerstones of modern neurodegenerative disease diagnosis, playing a key role not only in the initial diagnosis, but also in monitoring the progression of the condition.

Neuroimaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), or functional magnetic resonance imaging (fMRI), allow precise assessment of both structural and functional changes in the brain that are characteristic of diseases such as Alzheimer's, Parkinson's, or other neurodegenerative diseases.

Computed tomography (CT) or magnetic resonance imaging (MRI) are most commonly used to assess cortical atrophy. Both of these methods provide detailed images of brain structures, which are then analyzed using visual or computer methods [2]. Visual methods involve the evaluation of images by a specialist, who identifies structural changes based on experience, while computer methods, such as segmentation or volumetric analysis, allow for more accurate measurements of the degree of cortical atrophy and make it possible to monitor its progress over time.

In the past, the diagnosis of neurodegenerative diseases, especially the diagnosis of dementia, was mainly based on the exclusion of organic causes of cognitive impairment, such as brain tumors, vascular lesions or hydrocephalus. However, with the advent of modern imaging methods such as CT and MRI, the role of the neuroradiologist in the diagnosis of neurodegenerative diseases has been greatly expanded [3].

Nowadays, these techniques provide invaluable assistance in the process of comprehensive diagnosis and differentiation of various types of dementia, making it possible to precisely determine the location, severity and possible progression of structural changes in the brain.

**Imaging methods in the diagnosis of Alzheimer's disease**

Alzheimer's disease (AD) is the most common form of dementia and is characterized by progressive deterioration of cognitive function and behavior [28]. It is estimated that the number of people affected by AD worldwide will increase from 26.6 million in 2006 to 106.8 million

in 2050 [29, 30]. Although beta-amyloid (Aβ 1-42) is the main factor responsible for the development of the disease, other mechanisms such as oxidative stress, inflammatory processes, microglia activation, tau protein hyperphosphorylation and neurotransmitter dysfunction also contribute to cognitive impairment [30].

Prominent among the diagnostic methods that show great potential for detecting AD are magnetic resonance imaging (MRI) measurements of medial temporal lobe atrophy, PET imaging to assess glucose metabolism and beta-amyloid deposits, and analysis of biomarkers in cerebrospinal fluid (CSF).

In Alzheimer's disease, cortical changes are seen in specific regions of the brain. They mainly affect the temporal lobes (in the middle, inferior and temporal pole corners), parietal lobes (in the superior lobe, lateral part of the inferior lobe, precuneus and posterior part of the cingulate nerve) and frontal lobes (in the superior and inferior frontal regions) [32].

In contrast, in the process of normal brain aging, cortical atrophy most often affects the ostial fissures, cuneus, lateral occipital lobes, dorsomedial frontal lobe cortex, inferior frontal cortex, precentral cortex, posterior insula, and posterior spindle cortex [31].

In patients with AD, the lesions are located mainly in the medial and inferior parts and pole of the temporal lobes, the posterior part of the cingulate cortices and the pre-cingulate cortices. Cortical atrophy in both cases is also present in the same regions, such as the superior and angular corners and the lateral part of the superior frontal cingulate cortex [31].

Numerous studies have confirmed that MRI assessment of hippocampal atrophy can distinguish people with AD from healthy older adults with an accuracy of 80-90% [29]. Changes in this structure are not specific only to AD - they can also occur in aging, other neurodegenerative diseases, schizophrenia or bipolar affective disorder. What is characteristic of AD, however, is the location and severity of these changes [31].

Advanced imaging techniques allow assessment of the volume of individual hippocampal segments. In AD, atrophy most affects the head of the hippocampus, mainly the CA1 region, to a lesser extent other areas. In healthy subjects and those with mild cognitive impairment, the changes are usually localized in the CA4/D and subiculum regions. Changes in hippocampal volume are proportional to the severity of the disease, making them a valuable indicator for monitoring the progression of neurodegeneration and a potential tool for predicting CHA, especially in those with a heavy family history or at risk [31].

PET imaging with the 18F-FDG (fluoro-deoxyglucose) tracer is one of the key methods for assessing glucose metabolism in the brain, which has applications in the diagnosis of Alzheimer's disease (AD). Glucose, which is the main source of energy for neurons, reflects activity and function of different brain areas, and changes in its metabolism can indicate neurodegenerative processes.

With age, there is a natural decrease in blood flow and oxygen consumption in the brain, with a slight increase in the OGI (oxygen/glucose index).
In patients with Alzheimer's disease, PET with 18F-FDG shows a characteristic reduction in glucose metabolism in parietal-temporal areas, particularly in the hippocampus, with a less pronounced reduction in oxygen consumption in these regions. As a result, a significant increase in GI is found, which may be due to microcirculatory dysfunction impeding glucose transport and utilization. This dysfunction is associated with failure of the cholinergic system, as glucose is a substrate for acetylcholine synthesis [3].

**Advanced imaging in Alzheimer's disease**

Functional magnetic resonance imaging (fMRI), also known as BOLD MRI (Blood Oxygenation Level Dependent MRI), is a technique for assessing functional brain activity that is used widely in neurology, neurosurgery and psychiatry. The technique allows accurate mapping of the activation of different areas of the cerebral cortex during specific tasks, which is important for both diagnosis and planning of neurosurgical procedures. fMRI is particularly important in the evaluation of patients with cognitive disorders such as mild cognitive impairment (MCI) and dementia, enabling comprehensive analysis of both structural and functional changes in the brain [3].
The phenomenon used in this method involves a local increase in blood flow in activated brain areas, leading to a change in the ratio of oxyhemoglobin (oxygenated hemoglobin) to deoxyhemoglobin (reduced hemoglobin). This change causes an increase in signal intensity in T2-weighted images, which is recorded during scanning.
The fMRI study consists of two stages: the first, in which high-resolution structural images are obtained, and the second, in which the patient undergoes active or passive stimulation, leading to activation of specific brain regions [3].
Once the test is completed, the functional image is compared to the image at rest, allowing the creation of a map of the activity of the cortical centers involved in solving a specific task.

In fMRI studies of patients with mild Alzheimer's disease (AD) during memory tasks, greater activation of brain areas was observed compared to healthy subjects [33]. Similar results have also been obtained in carriers of the APOE gene, who are at increased risk of developing AD [34, 35].

There is hypothesis, that these results indicate the need to compensate for deficits memory by engaging broader areas of cortex in patients with cognitive impairment and genetically impaired individuals

Amyloid beta (Aβ) is a protein formed by enzymatic processing of amyloid precursor protein (APP), present in the cell membranes of neurons. Under pathological conditions, Aβ can accumulate as deposits, forming amyloid plaques, which are a characteristic marker of Alzheimer's disease (AD).

The development of methods that enable live imaging of amyloid plaques in the brain may represent a breakthrough in diagnosing mild cognitive impairment (MCI) and predicting its conversion to Alzheimer's disease.

Initial studies using these techniques have yielded promising results in AD patients. In particular, the use of a special tracer for PET, Pittsburgh Compound-B (PiB), which selectively binds amyloid, allowed visualization of brain areas affected by increased neurodegenerative changes. No increased accumulation of the tracer was found in control groups consisting of healthy subjects, confirming the specificity of this method for amyloid pathology in AD [36].

Single photon emission tomography (SPECT) allows assessment of regional blood flow in the brain through intravenous administration of radiopharmaceuticals such as technetium-99m in the form of hexamethyl-isopropylenoxime (Tc-99m-HMPAO) or ethylene-dicysteine dimer (Tc-99m-ECO). The radioisotopes cross the blood-brain barrier and accumulate in tissues in proportion to local blood flow, emitting gamma radiation that is recorded by a gamma-camera [36]. These images are subjected to qualitative, semi-quantitative or quantitative analysis. Semi-quantitative analysis, the most commonly used, includes assessment of interhemispheric asymmetry (significant differences in the >10%) and intrahemispheric blood flow deficits, with cerebellar or visual cortex perfusion as a reference [36].

It is now possible to combine SPECT with CT or MRI, allowing a more accurate anatomical assessment of blood flow abnormalities. Different types of dementia differ in the location and severity of hypoperfusion on SPECT. In Alzheimer's disease, reduced flow is observed in the

posterior temporal and parietal lobes. Frontotemporal dementia is characterized by an extensive decrease in perfusion in the frontal lobes and left temporal lobe, while vascular dementia shows patchy deficits corresponding to areas of ischemia [36].

**Imaging methods in the diagnosis of Parkinson's disease**

Parkinson's disease (PD), which is the second most common neurodegenerative disorder, is characterized by a significant loss of neurons within the nigrostriatal pathway, leading to a decrease in levels of dopamine [4], the neurotransmitter responsible for motor control. The clinical diagnosis of PD is based on the presence of typical motor symptoms, such as bradykinesia, muscle rigidity and resting tremor [5,6]. The importance of non-motor symptoms, which can occur in the early stages of the disease, is also increasingly . Nonetheless, making an early differential diagnosis can be difficult, especially when the initial disease picture includes symptoms shared with other conditions, such as spontaneous tremor, vascular parkinsonism, drug-induced parkinsonism or atypical syndrome, including multiple system atrophy and progressive supranuclear palsy. Often the diagnosis of PD is confirmed by a positive response to dopaminergic drugs, including levodopa. However, some patients with confirmed Parkinson's pathology show a poor response to treatment, while some people with other conditions, such as multisystem atrophy or progressive supranuclear palsy, respond to drug treatment. In the past, the misdiagnosis rate for idiopathic Parkinson's disease has been as high as 24% [7,8].

**Advanced MRI techniques in the diagnosis of Parkinson's disease**

Advanced MRI techniques for the diagnosis of Parkinson's disease offer new opportunities for early detection of brain changes that may indicate the stage of progression of this neurodegenerative disease. The use of modern imaging sequences, such as QSM, SWI and iron-sensitive techniques, allows precise mapping of brain structures that degenerate in Parkinson's disease, including the black matter (SN).

In addition, the neuromelanin (NM) imaging technique has become increasingly important for monitoring changes in the content of this pigment in the brain, which may be an important marker of the early stages of the disease.

With these advanced methods, it is possible not only to detect structural changes, but also to differentiate Parkinson's from other neurodegenerative conditions, such as spontaneous tremor or atypical parkinsonism.

Parkinson's disease (PD) is a neurodegenerative motor disorder whose primary cause is the loss of dopaminergic neurons in the black matter (SN). Black matter is a brain structure that plays a key role in regulating body movements through the production of dopamine, a neurotransmitter that enables the transmission of signals between different areas of the brain responsible for motor control. The black matter is divided into two parts: the reticular part of the (SNpr) and the dense part (SNpc), of which the SNpc contains dopaminergic neurons. In Parkinson's disease, there is a degeneration of neurons in this part of the brain, which leads to a dopamine deficiency and, as a result, difficulties in coordinating movements, manifested by tremors, muscle rigidity and slowed movements, among other things.

The structure of the black matter is very complex, and within the SNpc there are subregions called nigrosomes. These are areas with a particularly high density of dopaminergic neurons and a relatively low concentration of iron. Degeneration of these nigrosomes in Parkinson's disease is one of the key processes leading to motor symptoms, as their damage exacerbates dopamine deficits, making it difficult to precisely control body movements [9,10].

High-quality MRI imaging, using strong magnetic fields (above three Tesla) and iron-sensitive sequences such as T2* and SWI (susceptibility weighting), allows accurate visualization of structures in the brain.

The T2* sequence is particularly sensitive to the presence of iron and can reveal lesions that are difficult to detect with traditional MRI methods. The SWI technique, on the other hand, by exploiting differences in the magnetic susceptibility of tissues, allows imaging of microscale brain lesions, such as microbleeds or iron accumulation in areas of the brain responsible for motility.

Nigrosome-1, which is part of the black matter, appears in these images as a bright, egg-shaped structure in the upper part of the SNpc. Because of its shape, which resembles the tail of a swallowtail, some authors call it the "swallowtail sign" [11]. In Parkinson's disease, where there is degeneration of dopaminergic neurons, withinthe nigrosomes there is an increase in iron content, and in the case of nigrosome-1, these changes are particularly prominent and appear early.From this reason, the dovetail sign becomes invisible in MRI images in Parkinson's patients, which has been confirmed in numerous studies and analyses comparing patients with the disease and healthy subjects [12,13].

Neuromelanin (NM) is a specific pigment protein that is found mainly in areas of the brain associated with movement regulation, such as the black matter (SN) and locus coeruleus (LC).

Its presence and changes in quantity can provide valuable clues in the diagnosis of neurodegenerative diseases, especially Parkinson's disease.

For this reason, neuromelanin imaging has become an important tool in differentiating Parkinson's disease from other forms of parkinsonism and early detection of pathological changes in the brain.

It is formed by oxidation of dopamine and has the ability to bind iron and other metals. When cells die, extracellular neuromelanin can contribute to inflammatory processes in the brain. The amount of neuromelanin changes with age and is an important marker in the diagnosis of Parkinson's disease (PD) and in differentiating PD from other movement disorders, such as essential tremor (ET) or atypical parkinsonism [14] . With MRI sequences that take advantage of the paramagnetic properties of neuromelanin, it is possible to accurately image its amount in the brain.

Studies have shown that reduced neuromelanin in SN and LC can be used to differentiate PD patients from healthy individuals and to detect the early stages of the disease. In the future, neuromelanin may become an important marker for early detection of Parkinson's disease and its differentiation from other neurodegenerative conditions [15,16].

Iron, like neuromelanin, is present in various parts of the brain, including the black matter (SN) and locus coeruleus (LC). In healthy individuals, the amount of iron in the brain changes with age - it remains constant in the LC, while it increases in the SN.

In Parkinson's disease (PD), it has been noted that too much iron accumulates in the brain, especially in areas such as the black matter [17]. This accumulation can lead to neuronal damage and other problems within the brain, which can worsen the symptoms of the disease.

Modern imaging techniques, such as magnetic resonance imaging (MRI), make it possible to detect and accurately measure iron concentrations in the brain. Using special MRI sequences such as T2* and R2*, researchers are able to see changes associated with iron accumulation in areas such as the black matter. The research shows that iron accumulation in the brains of Parkinson's patients is clearly visible and can help assess the progression of the disease. In addition, precision techniques such as QSM can provide even more accurate information, making it a promising tool in the diagnosis and monitoring of Parkinson's disease [18,19].

The next advanced magnetic resonance imaging technique is diffusion tensor imaging (DTI), which finds application in monitoring the progression of Parkinson's disease (PD), correlating microstructural changes with clinical symptoms, and differentiating atypical parkinsonisms. By analyzing the diffusion of water molecules in white matter, DTI makes it possible to assess the

integrity of neuronal pathways and structural changes in key areas of the brain, such as the black matter, brainstem and connections within the basal nuclei. Studies have shown that DTI can provide objective indicators of neuronal pathway damage in advanced stages of PD and help assess disease subtypes [25,26].

However, the clinical application of DTI comes with a number of limitations.

First, changes in DTI parameters, such as FA (Fractional Anisotropy) or MD (Mean Diffusivity), are not specific and may only indirectly reflect pathological processes, making it difficult to interpret the results unambiguously.

Second, standard clinical DTI protocols have limited spatial resolution, which affects the accuracy of assessing small structures such as the black matter or sinusoidal site [27].

In addition, technical challenges such as noise, distortion, and fiber crossing issues can lead to errors in analyzing the results.

Further studies are needed to confirm the utility of DTI in assessing the correlation of PD symptoms with specific anatomic lesions and in monitoring disease progression.

**Advanced neuroimaging techniques in the diagnosis of Parkinson's disease**

In recent years, the development of advanced neuroimaging techniques, such as PET (positron emission tomography) and SPECT (single-photon emission tomography), has significantly expanded our knowledge of the degenerative processes involved in Parkinson's disease (PD) and other movement disorders. Thanks to these technologies, it has become possible to monitor in detail changes in brain dopamine metabolism, dopamine uptake and the function of dopaminergic transporters, allowing for more accurate diagnosis and monitoring of the disease [20].

One of the most commonly used PET tracers in the diagnosis of PD is 18F-FDOPA, which allows assessment of the activity of aromatic amino acid decarboxylase (AADC, which converts 18F-FDOPA (a radioactive isotope) into 18F-dopamine, and dopamine turnover in the striatum. This tool allows monitoring the density of dopaminergic axon terminations.

In contrast, the availability of presynaptic dopamine transporters (DATs) can be accurately assessed using tropane-based markers. The dopamine transporter plays a key role in regulating dopamine levels in the synaptic space, and its assessment is an important marker for assessing the integrity of the dopaminergic system in PD [21,22].

Another potential indicator for the early diagnosis of Parkinson's disease (PD) is the evaluation of abnormalities in cardiac sympathetic innervation by SPECT using iodine-labeled metaiodobenzylguanidine (123I-MIBG). MIBG, as a precursor to norepinephrine, allows analysis of the function of the postganglionic fibers of the sympathetic nervous system [23]. In PD patients, studies have shown reduced myocardial MIBG uptake, indicating damage to sympathetic innervation. Importantly, these changes are present early in the course of the disease, even in individuals who show no signs of autonomic dysfunction.

Unlike PD, other neurodegenerative diseases, such as multisystem degeneration (MSA) or progressive supranuclear palsy (PSP), do not have similar MIBG uptake abnormalities. Thus, this method can be useful in differential diagnosis and in identifying disease Parkinson's at a very early stage, even before the appearance of motor symptoms [24].

**Advantages and limitations of advanced imaging methods in the diagnosis of neurodegenerative diseases**

Advanced brain imaging methods, such as MRI, fMRI, PET and SPECT, are the cornerstone of modern diagnosis and monitoring of neurological diseases. These methods offer a number of advantages, including high-precision imaging of brain structures, which makes it possible to detect subtle changes in brain tissue, such as neuronal atrophy or the presence of pathological foci that may be indicative of neurodegenerative diseases such as Alzheimer's or Parkinson's. MRI provides accurate information about anatomical changes, enabling the assessment of structural brain damage, while fMRI provides the ability to monitor brain activity in real time, which is crucial for analyzing neuropsychological function and studying the interaction of different brain areas. PET, on the other hand, allows imaging of metabolic processes, such as glucose metabolism or changes in receptor activity, making it possible to detect pathological metabolic changes even before the onset of clear clinical symptoms. SPECT, although relatively less precise than PET, offers advantages in analyzing blood flow and brain function in diseases such as stroke and vascular disease. These technologies allow for early diagnosis, enabling faster implementation of appropriate treatment and therapy, which in turn can delay disease progression and improve patients' quality of life.

However, despite their many advantages, advanced brain imaging methods also have their limitations. The cost of these tests, both in terms of equipment and diagnostic procedures, remains a high challenge, limiting the availability of these technologies, especially in countries. In addition, some of the methods, such as fMRI, have their limitations in terms of temporal

resolution, making them not always capable of accurately tracking very rapid changes in brain activity. PET and SPECT are invasive technologies, requiring the use of radioisotopes, which carries radiation exposure risks. In addition, interpretation of imaging results can be complicated because changes detected in the images may not always correlate with a patient's clinical symptoms, which can lead to difficulties in diagnosis.

Despite these limitations, advanced imaging methods have great potential for the diagnosis, treatment and monitoring of neurological diseases.

## Summary

Advanced brain imaging modalities, such as magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission tomography (SPECT) and functional magnetic resonance magnetic resonance (fMRI), represent a key tools in the diagnosis and monitoring of neurodegenerative diseases. They allow precise assessment of both structural and functional changes in the brain, which makes it possible to detect pathology early, monitor disease progression and assess the effectiveness of therapy. While each of these methods offers significant benefits, their use also comes with certain limitations, such as high cost, limited availability, and potential risks associated with the use of radioactive substances. In the face of these challenges, further advances in imaging technology, as well as the use of new analytical tools such as artificial intelligence, could help make these methods more effective and accessible in the diagnosis of neurodegenerative brain diseases.

## Disclosure

### Author's contribution

Conceptualization: Paulina Dorota Pietrukaniec; Methodology: Katarzyna Kamińska-Omasta Software: Kuba Borys Romańczuk; Check: Szymon Przemysław Stolarczyk and Daria Rybak; Formal analysis: Kinga Furtak and Olga Krupa; Investigation: Bartosz Omasta and Magdalena Agata Czerska; Resources: Zofia Martyna Wójcik and Bartosz Omasta; Data curation: Daria Rybak; Writing - rough preparation: Olga Krupa;

Writing – review and editing: Paulina Dorota Pietrukaniec and Kinga Furtak; Visualization: Zofia Martyna Wójcik and Szymon Przemysław Stolarczyk; Supervision: Katarzyna Kamińska-Omasta; Project administration: Bartosz Omasta and Kuba Borys Romańczuk; Receiving funding - no specific funding.

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