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Nuclear Medicine Investigations in Dementia and Parkinsonism

Nuklearnomedicinske preiskave pri diagnosticiranju demence in parkinsonizmov

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Abstract

The incidence of neurodegenerative brain disorders, manifested as dementia or parkinsonism, is increasing with population aging. Early and correct diagnosis is essential for excluding potentially curable causes, optimizing symptomatic treatment, social care and selecting patients for clinical trials. Final diagnosis of most neurodegenerative brain diseases can only be made by histopathological examination of the brain tissue. However, functional nuclear-medicine investigations contribute greatly to the diagnosis *in vivo*. Changes in regional brain metabolism, neurotransmitter system dysfunction and misfolded protein deposition can be observed. Based on specific changes in regional brain metabolism measured with ^{18}F-FDG PET, we can distinguish between Alzheimer's disease, dementia with Lewy bodies and frontotemporal dementia, and between Parkinson's disease and other neurodegenerative parkinsonisms. Dopaminergic system imaging (e.g. dopamine transporter scintigraphy, DaTSCAN) enables us to discriminate neurodegenerative parkinsonism from alternative causes. Excessive deposition of amyloid-β, a pathological hallmark of Alzheimer's disease, can be identified by amyloid PET already in preclinical subjects. Nuclear medicine imaging methods, indications, characteristic findings and limitations of these investigations in neurodegenerative brain disorders are presented in this article.

Izvleček

Nevrodegenerativne bolezni možganov, ki se klinično izrazijo kot demenca ali parkinsonizem, postajajo s staranjem prebivalstva vse pogostejše. Zgodnja in pravilna postavitev diagnoze je pomembna zaradi izključevanja ozdravljivih vzrokov, ustreznega simptomatskega zdravljenja, socialnih ukrepov in vključevanja bolnikov v klinične raziskave. Povsem dokončno diagnozo večine nevrodegenerativnih bolezni možganov lahko postavimo le na podlagi patohistološkega vzorca možganovine. Za živa pa so nam v veliko pomoč funkcijske nuklearnomedicinske preiskave, s katerimi lahko prikažemo spremenjeno področno presnovo možganov, motnje na ravni nevrotransmitrskih sistemov in patomorfološki substrat bolezni – tj. kopičenje patoloških beljakovin. Glede na značilne spremembe regionalne presnove možganov, ki jih preučujemo s pozitronsko emisijsko tomografijo (PET) možganov z radioaktivnim fluorom (^{18}F) označene deoksiglukoze, lahko razlikujemo med Alzheimerjevo boleznijo, demenco z Lewyjevimi telesci, frontotemporalno demenco in redkejšimi vzroki kognitivnega upada ter med Parkinsonovo boleznijo in drugimi nevrodegenerativnimi parkinsonizmi. Z ugotavljanjem integritete dopaminergičnega sistema (npr. scintigrafijo dopaminskega prenašalca, DaTSCAN) lahko razlikujemo med nevrodegenerativnimi parkinsonizmi in drugimi možnimi vzroki težav. Amiloidni PET možganov nam prikaže prisotnost in značilno razporeditev čezmernega kopičenja amiloida pri bolnikih z Alzheimerjevo boleznijo že pred pojavom kliničnih znakov bolezni. V prispevku predstavljamo nuklearnomedicinske preiskave, obravnavamo indikacije in značilne spremembe ter omejitve teh preiskav pri diagnosticiranju nevrodegenerativnih bolezni možganov.

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1 Introduction

Disease processes of the nervous system, which are characterized by progressive degeneration of neurons, are termed neurodegenerative disease. Clinically, neurodegenerative brain diseases are most commonly expressed by cognitive decline and/or movement disorders (1). Their common pathogenetic mechanism is the accumulation of pathological proteins in the nervous system that damage neurons and their connections (2).

The definitive diagnosis of neurodegenerative parkinsonisms can be made by histopathological examination of a brain tissue after the patient's death. For the living, the diagnosis is based on the clinical picture, but the results of imaging tests may also be helpful. In the diagnosis of dementia, biological markers are gaining ground, with the help of which we can already prove pathological processes in the brain *in vivo*. Thus, we know the markers of neurodegeneration, accumulation of pathological proteins – amyloid beta and tau protein (3).

Correct and early clinical diagnosis is important, as it determines the choice of treatment, outcome prediction, long-term plans of the patient and relatives and, last but not least, the selection of appropriate patients for research, which can significantly contribute to the success of clinical trials (4,5). In addition to clinical neurological and neuropsychological examination, laboratory tests of blood and cerebrospinal fluid, structural imaging and, in some cases, neurophysiological examinations, functional imaging methods also help in making a diagnosis. Positron emission tomography (PET) using fluorine-18-labeled fluorodeoxyglucose (^{18}F-FDG) can be used to study the metabolism or synaptic activity of the brain and thus demonstrate possible neurodegeneration in the brain. Other functional imaging studies may show the integrity of neurotransmitter systems (e.g., dopamine transporter or dopamine receptor scintigraphy) or the accumulation of pathological proteins (e.g., amyloid beta and tau protein) (6). Brain activity can also be studied indirectly through changes in cerebral blood flow by functional magnetic resonance imaging (MRI) or perfusion scintigraphy.

The article contains an overview of imaging methods, especially functional nuclear-medicine investigations, used in diagnosing neurodegenerative diseases of the brain, which are divided into two groups based on the predominant symptoms: dementia and parkinsonism (1).

1.1 ^{18}F-FDG PET of the brain

A brain PET with ^{18}F-FDG (^{18}F-FDG PET) is a nuclear medicine imaging method most commonly used in clinical practice to diagnose oncological, inflammatory and infectious as well as cardiac diseases (7), and in the last decade it has become the gold standard in diagnosing neurodegenerative brain diseases as well (8-10).

The ^{18}F-FDG radiopharmaceutical is a structural analogue of glucose, which is the main energy substrate of brain cells. The accumulation of ^{18}F-FDG in the brain is due to high glucose uptake in neurons

and astrocytes. Upon uptake into brain cells, ^{18}F-FDG is phosphorylated by the enzyme hexokinase. ^{18}F-glucose-6-phosphate is no longer metabolized and remains trapped in cells, allowing us to demonstrate the metabolic activity of the brain using PET. The uptake of ^{18}F-FDG in the brain is closely related to neuronal synaptic activity, especially in the area of the gray matter and basal ganglia, and represents the metabolic activity of the brain (11). In patients with neurodegenerative diseases, functional changes in ^{18}F-FDG PET of the brain usually appear several years before the visible signs of atrophy in structural brain imaging with computed tomography (CT) and MRI tomography (12).

^{18}F-FDG PET of the brain is used in clinical practice in diagnosing dementia or cognitive impairment (8,10) and parkinsonism (9), in which we can distinguish many syndrome-specific patterns of ^{18}F-FDG accumulation, connected to the clinical picture. The role of CT in ^{18}F-FDG PET is particularly important for correcting the attenuation of PET images, while allowing us anatomical coregistration; for this purpose, we use the so-called localisation or low-dose CT. All modern PET/CT devices also enable capturing CT images in diagnostic quality, although the main purpose of the ^{18}F-FDG PET examination is to define the functioning of individual areas of the brain. However, the role of diagnostic CT in these diseases is limited primarily to the exclusion of other disease states (e.g. brain tumors).

^{18}F-FDG PET of the brain in Slovenia is performed in accordance with the guidelines of the European Association of Nuclear Medicine (EANM) (13). Patients need to fast for at least four hours before the examination, be able to cooperate (i.e. lie still for at least 45 minutes) and must not have severe claustrophobia.

For optimal performance of the test, it is crucial that blood sugar (BS) levels are properly regulated prior to ^{18}F-FDG intake. Our center has set a limit of <10 mmol/l, and the guidelines recommend a limit of BS <160 mg/dl, which is approximately 9 mmol/l (13). Namely, the high level of BS reduces the uptake of ^{18}F-FDG in the brain, which can result in the final PET images of poorer quality for diagnostic purposes. At BS levels > 10 mmol/l, the test may be performed with appropriate preparation of the patient with a short-acting insulin.

After intravenous radiopharmaceutical administration, patients have to lie still for 30 minutes in a darkened room with their eyes open (13), which is followed by imaging that lasts 10-15 minutes. For an optimal result of the examination, it is recommended that it be prepared jointly by a nuclear medicine specialist and a neurologist.

1.2 Visual representation of the integrity of the dopaminergic system

In addition to changes in brain metabolism, the integrity of the dopaminergic system can also be determined in neurodegenerative diseases using nuclear medicine imaging methods. In parkinsonisms, dopaminergic neurons in the substantia nigra, of which nerve endings project into the striatum, deteriorate. The decline of dopaminergic neurons and the associated presynaptic impairment of the dopaminergic system can be demonstrated *in vivo* by radiopharmaceuticals that bind to presynaptic neurons in the striatum or they are selectively adopted by them (14). The ^{18}F-fluorodopa radiopharmaceutical demonstrates the activity of dopa decarboxylase and the ability to store dopamine in presynaptic neurons (14). A similar data on the state of the presynaptic dopaminergic system is obtained with the use of radiopharmaceuticals that selectively bind to the dopamine transporter on presynaptic neurons (dopamine transporter, DAP). For clinical purposes, the European Medicines Agency (EMA) and the U.S. Federal Food and Drug Administration (FDA)

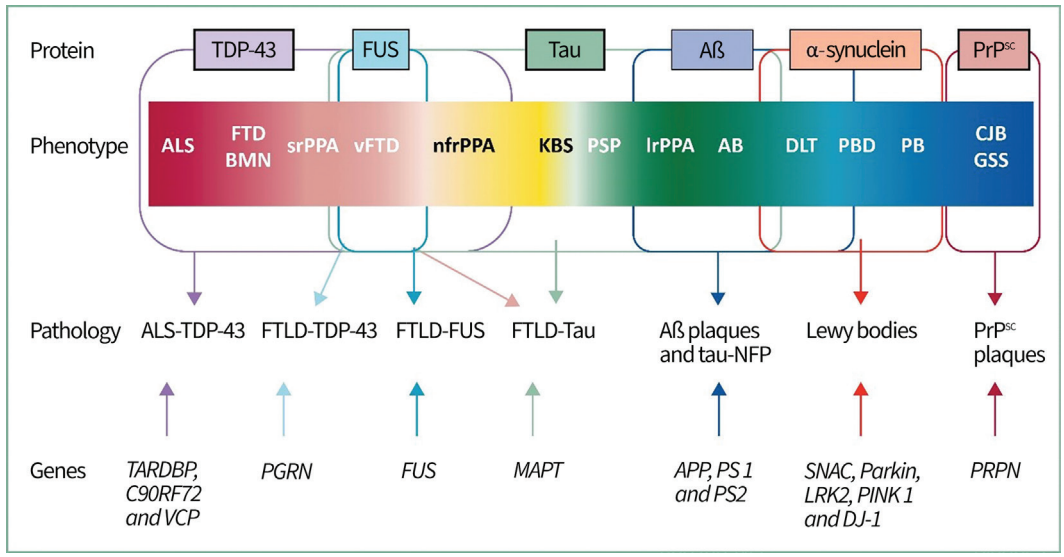

Figure 1: Genetic, pathological and clinical continuum of neurodegenerative diseases - proteinopathies. Diseases associated with individual proteins, pathological substrates and genes that directly or indirectly affect the deposition of a single protein in the brain are presented. Overlap of proteinopathies in various clinical syndromes is evident. ALS - amyotrophic lateral sclerosis. FTD MND – frontotemporal dementia with motor neuron disease, svPPA - semantic variant of primary progressive aphasia, bFTD – behavioral variant frontotemporal dementia, nfvPPA – nonfluent variant of primary progressive aphasia, CBS – corticobasal syndrome, PSP – progressive supranuclear palsy, lvPPA – logopenic variant of primary progressive aphasia, AD – Alzheimer's disease, DLB – dementia with Lewy bodies, PDD – Parkinson's disease with dementia, PD – Parkinson's disease, CJD – Creutzfeldt-Jakob disease, GSS - Gerstmann–Sträussler–Scheinker syndrome, NFP – neurofibrillary tangles. Adapted from Villemagne, 2015 (18).

have approved the radiopharmaceutical ^{123}I-ioflupane (123I-β-CIT-FP) - the proprietary name DaTSCAN, which is also routinely used in Slovenia. The third target protein that can be used to study the density of presynaptic neurons is the vesicular monoamine transporter 2 (VMAT2), a protein complex on the membrane of neurotransmitter vesicles that is involved in the transmission of monoamine neurotransmitters, including dopamine (15).

For research purposes, the integrity of postsynaptic dopaminergic neurons in the basal ganglia can also be studied with radiopharmaceuticals that bind to the dopamine D2 receptor: ^{11}C-racloprid and 123I-iodobenzamide (IBZM) (14,16). Although we can to some extent distinguish between Parkinson's disease (PD) and other neurodegenerative parkinsonisms on the basis of this examination, this imaging has a much lesser differentiating power than ^{18}F-FDG PET of the brain (17) and is not used for the purpose of distinguishing between parkinsonisms.

1.3 Visual representation of pathological proteins in the brain

Neurodegenerative diseases are characterized by the deposition of various pathological proteins at specific sites in the brain. Amyloid beta, tau, and alpha-synuclein (α-syn) are most commonly involved in the pathophysiological process. Amyloid beta is deposited in the brain in cerebral amyloid angiopathy and together with the tau protein in Alzheimer's disease (AD). Tauopathies, or diseases in which the tau protein accumulates excessively, include frontotemporal dementia (FTD), corticobasal degeneration (CBD) and

progressive supranuclear palsy (PSP) (the latter two diseases are clinically classified as so-called parkinsonisms plus). α-syn is deposited in the brain in PD, dementia with Lewy bodies (DLB), and in multiple system atrophy (MSA) (2). Thus, the accumulation of a certain protein is not characteristic of only one disease or syndrome, but pathological proteins can accumulate in various combinations in various neurodegenerative syndromes. Thus, we can talk about a continuum of proteinopathies with different clinical pictures (Figure 1) (18).

Until recently, direct evidence of individual protein deposition was possible only by histopathological examination of a brain sample by immunohistochemical methods. Based on these methods, several groups have developed radiopharmaceuticals that bind to pathological proteins *in vivo*. The first radiopharmaceutical that specifically binds to amyloid beta was developed at the turn of the millennium, the so-called *Pittsburgh compound B* (^{11}C-PiB) (19). Due to technical limitations (marked with the short-lived radioactive element ^{11}C), ^{11}C-PiB can only be used in establishments that have a cyclotron in the immediate vicinity. In recent years, the EMA and the U.S. FDA have approved the use of three ^{18}F-labeled radiopharmaceuticals that bind to amyloid beta for clinical use: ^{18}F-flutemetamol, ^{18}F-florbetaben, and ^{18}F-florbetapir (20-22). The use of ^{18}F-labeled radiopharmaceuticals, which have a longer half-life (110 minutes) and can therefore be transported to facilities up to a few 100 km from the cyclotron, has enabled the transition from amyloid imaging to clinical practice.

The development of radiopharmaceuticals that bind to the tau protein is more complex, as the protein is located within nerve cells and exists in six isoforms. Tau is modified posttranslationally in various ways. It is deposited in different fibrillar forms, in different cells and areas of the brain (23). Several molecules are used for research purposes (the most common are ^{18}F-AV1451, ^{18}F-THK5317, ^{18}FTHK5351 and ^{11}C-PBB3 (6)), the most researched use in the diagnosis of AD, and slightly less in the diagnosis of other tauopathies (CBD, PSP, FTLD- 17) (23).

The development of radiopharmaceuticals with α-syn binding (PB, MSA, DLB) is still ongoing. The problem is mainly in the specificity of the radiopharmaceutical and the pharmacokinetic properties of the molecules used so far. In addition, the concentration of α-syn in the brain in alpha-synucleopathies, i.e. diseases in which excessive accumulation of α-syn occurs, is relatively low, which may present a problem in capturing PET images (24).

1.4 Reading nuclear medical examinations of the brain

The evaluation of ^{18}F-FDG PET in the brain for clinical diagnostic purposes involves specialists in nuclear medicine and neurology. After a visible (qualitative) evaluation of the image, we also use statistical methods for image analysis. Images of an individual or a group of patients are compared with healthy subjects or with another group of patients. A precondition for comparison is spatial normalization, in which the image of an individual is spatially adapted to the general pattern. Using univariate methods, among which statistical parametric mapping (SPM (25)) is most often used, we compare individual "voxels" of both groups of subjects and present the result in the form of normalized t- or z-maps (Figure 2a). The spatial distribution of changes is even more telling if the result obtained in this way is stereotactically projected onto the cerebral cortex, which is enabled by, for example, 3D-SPP Neurostat software (Three-dimensional Stereotactic Surface Projections (26). See Figure 2b). Similar softwares for statistical image processing are also included in software packages provided by gamma and PET camera manufacturers (e.g. Scenium, Siemens Molecular Imaging Ltd.).

Using more advanced multivariate

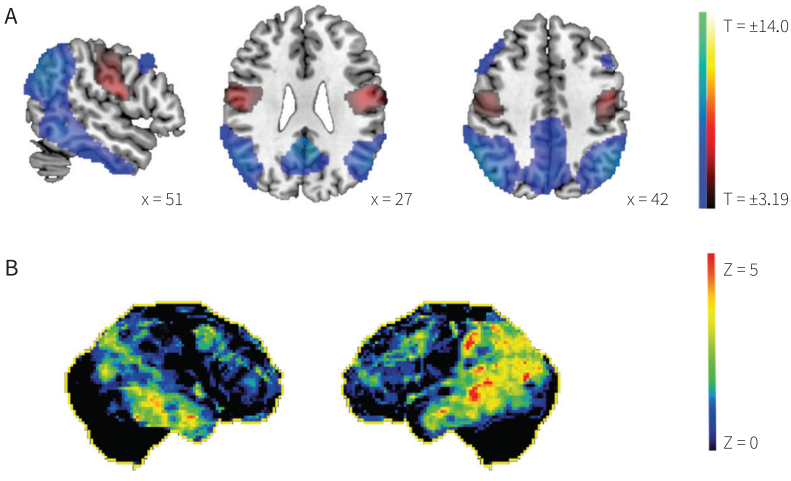

Figure 2: Demonstration of differences between Alzheimer's disease patients and healthy subjects using statistical methods. A –Statistic parametric mapping, SPM; SPM12 variant, comparison between 48 patients with AD and 40 healthy subjects, blue areas represent relatively reduced and red areas relatively increased brain metabolic activity, p = 0,001) (source: Department of Nuclear Medicine, UMC Ljubljana), B – stereotactic projection of statistical differences in brain metabolism between a patient with AD and a group of healthy subjects on the cerebral cortex (Neurostat 3D-SPP); only areas with relatively reduced metabolic activity are presented (source: Department of Nuclear Medicine, UMC Ljubljana).

analysis of ^{18}F-FDG PET of the brain, specific metabolic patterns of functionally related areas of the brain can be identified as syndrome. One such method is multivariate network analysis based on scaled subprofile mapping - principal component analysis, SSM-PCA (27). (See Figure 8). This method is intended to identify samples as well as to prospectively monitor the expression of metabolic samples in individual subjects (28).

2 The role of nuclear medicine in diagnosing dementia of ^{18}F-FDG PET of the brain

2.1 Alzheimer's disease

AD is the most common neurodegenerative brain disease and the most common cause of dementia. It mostly affects people over the age of 65 (1). The number of patients in Slovenia is estimated at around 25,000 people (29). Clinically, the disease is characterized by a progressive cognitive decline, which is initially manifested by impaired short-term memory and visual-spatial orientation, but gradually impairs all cognitive functions, leading to disability. This puts a huge burden on relatives, the health care system and society at large. Disease processes in the brain begin decades before the onset of dementia.

A summary of typical changes in brain metabolism in AD in ^{18}F-FDG PET of the brain is presented in Table 1 and Figure 3B (8,10,30).

The changes first appear in the posterior cingulate gyrus (31). With progression, characteristic parieto-temporal hypometabolism occurs (Table 1), and with advanced disease, there is also a decline in metabolism in the prefrontal cortex. The changes are usually asymmetric and affect the posterior parts of the neocortex the most.

With the help of ^{18}F-FDG PET of the brain, the course of AD can be monitored, as with the progression of the disease, the areas of reduced metabolism expand to a larger area of the neocortex, and the decline becomes more pronounced. The use of ^{18}F-FDG PET of the brain, in addition to early diagnosis, also helps to differentiate between different types of dementia, the clinical picture of which, especially in the early stages of the disease, may overlap (32).

In patients with mild cognitive impairment (MCI), ^{18}F-FDG PET of the brain allows us to predict progression to dementia with approximately 90% sensitivity and specificity (33). In patients with MCI as part of AD, hypometabolism is observed in areas typical of AD (Table 1) (31).

AD subtypes, such as posterior cortical atrophy (PCA) and the logopenic variant of primary progressive aphasia (lvPPA), have a characteristic distribution of metabolic changes. In PCA, we find hypometabolism of the occipital cortex, which largely coin-

cides with hypometabolism in DLB (34). The two syndromes can be distinguished by imaging a dopamine transporter (e.g. DaTSCAN), which is preserved in AD and PCA and defective in DLB (35,36). LvPPA is characterized by hypometabolism of the left temporal lobe (upper, middle, and lower temporal gyrus), left superior and inferior parietal lobe, and prekuneus (37). Metabolic changes in other forms of primary progressive aphasia are described in the chapter on frontotemporal dementias.

2.2 Dementia with Lewy bodies

DLB is the second most common neurodegenerative dementia in patients older than 65 years (1,36). It is characterized by a fluctuating course of cognitive impairment, parkinsonism, visual hallucinations early in the course of the disease, hypersensitivity to neuroleptics and sleep disorders in the REM phase (36).

A marked damage to the occipital lobes helps us to distinguish from AD with a sensitivity of 83–90% and a specificity of 80–87% (32,38). In addition, the relatively preserved glucose metabolism in the posterior part of cingulate gyrus (cingulate island sign) (39) and in the medial temporal lobe (in the hippocampus) (40) helps to distinguish from AD. The typical distribution of metabolic changes seen in DLB with ^{18}F-FDG PET of the brain is presented in Table 2 and Figure 3C.

Table 1: Metabolic characteristics of Alzheimer's disease.

Reduced accumulation of radiopharmaceuticals in:
parietal lobe,
posterior temporal lobe,
posterior cingulate gyrus,
precuneus,,
medial temporal lobe and
prefrontal cortex (in advanced disease).
Preserved accumulation of radiopharmaceuticals in:
basal ganglia,
thalamus,
cerebellum,
primary sensory-motor cortex and
occipital lobe.

2.3 Parkinson's disease with dementia

Patients with PD often develop dementia late in the course of the disease; after 20 years of illness, it is present in as many as 83% (41) of patients; we are talking about PD with dementia (PDD).

Patients with PDD have decreased ^{18}F-FDG uptake in different areas of the cerebral cortex. In the case of patients with PD without dementia, they have more pronounced hypometabolism in the parietal and frontal cortex (42).

The metabolic characteristics of PDD overlap in part with DLB. The distinction between PDD and DLB is possible mainly on the basis of glucose hypometabolism in the occipital lobe, which is usually much more pronounced in patients with DLB. An additional distinction between DLB and PDD is also made possible by hypometabolism of the lateral temporal cortex, which is less pronounced in PDD than in DLB. Nevertheless, the distinction between the two diseases is sometimes complicated and unreliable with the ^{18}F-FDG PET examination of the brain. They are distinguished mainly clinically according to the time course of the onset of movement disorders and cognitive decline. In DLB, the latter often occurs before the movement disorder or no later than one year after the onset of movement problems. Clinical and metabolic similarities between the two diseases are not surprising, as both cases involve alpha-nucleinopathy with accumulation of Lewy bodies in the cerebral cortex.

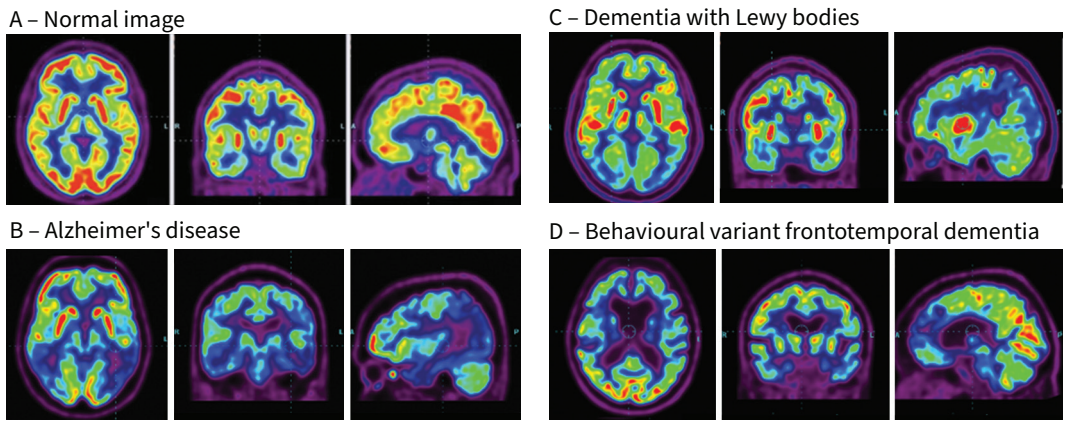

Figure 3: ^{18}F-FDG PET of the brain in (A) a healthy subject, (B) a person with Alzheimer's disease, (C) dementia with Lewy bodies, and (D) behavioral variant frontotemporal dementia (source: Department of Nuclear Medicine, UMC Ljubljana).

2.4 Frontotemporal dementia

In patients under 65 years of age, FTD is the second most common form of dementia after AD (1). Clinically, it is characterized by personality change and cognitive decline with impaired attention, speech, and executive functioning abilities. According to the clinical picture, we divide FTD into behavioural variant (bFTD) and two forms of primary progressive aphasia (PPA): nonfluent (nfvPPA) and semantic variant of PPA (svPPA).

Distinguishing between AD and bFTD (Figure 3C) using the ^{18}F-FDG PET examination of the brain is easy in most cases. The typical distribution of metabolic changes detected by ^{18}F-FDG PET of the brain in the three FTD subtypes is presented in Table 3 (37,43-47).

Table 2: Metabolic characteristics of dementia with Lewy bodies.

Reduced accumulation of radiopharmaceuticals in:
• primary visual cortex,
• occipital association cortex and
• less pronounced in the parietal and frontal cortex and the anterior cingulate gyrus.
Preserved accumulation of radiopharmaceuticals in:
• basal ganglia,
• thalamus,
• cerebellum,
• cerebellum,
• medial temporal lobes and
• posterior cingulate gyrus (cingulate island sign).

2.5 Vascular Dementia

The diagnosis of vascular dementia is usually made on the basis of a clinical picture in the presence of vascular changes in morphological imaging examinations (CT and MRI). In specific circumstances, it makes sense to perform ^{18}F-FDG PET of the brain to detect the concomitant presence of AD or other neurogenerative diseases (30).

The pattern of accumulation of the radiopharmaceutical depends on the size and blood flow of the affected vessels. If a larger cerebral artery is affected, the metabolic failure will be seen in the affected blood flow in line with the changes in the structural images (48). In the subcortical structure impairment due to multiple infarcts, the pattern of ^{18}F-FDG accumulation may be highly variable and will usually correlate with ischemic changes seen

on morphological imaging. Compared to AD, vascular dementia is characterized by a different pattern with reduced accumulation subcortically and in the primary sensorimotor cortex, whereas the association areas are less affected (49).

2.6 Sporadic Creutzfeldt-Jakob disease

Sporadic Creutzfeldt-Jakob disease (CJD) is a rare rapidly progressive neurodegenerative disease that results from the deposition of pathological prion protein in the brain. It manifests clinically as a rapidly progressive cognitive decline that progresses to akinetic mutism as the disease progresses (50). ^{18}F-FDG PET of the brain shows extensive areas of cerebral hypometabolism, which may be relatively asymmetric and most pronounced in the frontal, parietal lobes (primarily medial), in the head of the caudate, and in the thalamus. The metabolism of the temporal lobe and cerebellum is relatively preserved (51).

Table 3: Characteristics of the most common subtypes of frontotemporal dementia (FTD) on ^{18}F-FDG PET of the brain. bFTD - behavioral variant of FTD (44 46), svPPA - semantic variant of primary progressive aphasia (PPA) (37,47), nfvPPA - non-fluent variant of PPA (43).

bFTD:
Reduced accumulation of radiopharmaceuticals in:
frontal lobes (orbitofrontal, frontopolar, medial frontal, dorsolateral, lateral inferior frontal and in anterior cigulate gyrus);
temporal lobes and subcortical structures of the gray matter (advanced disease).
svPPA:
Reduced accumulation of radiopharmaceuticals in:
left anterior temporal lobe.
nfvPPA (relatively heterogeneous group):
Reduced accumulation of radiopharmaceuticals in:
left frontal cortex (lower and middle frontal, dorsolateral prefrontal and frontopolar cortex, Broca's area);
left temporal cortex (Wernicke's area, middle and inferior temporal regions);
in the initial stages of the disease hypometabolism of the left insula and frontal opercular region.
in the initial stages of the disease hypometabolism of the left insula and frontal opercular region.
hippocampus and amygdaloid nucleus.

3 Visual representation of pathological protein accumulation in the brain

3.1 Amyloid brain imaging in the diagnosis of dementia

The basic pathomorphological features of AD are intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein and amyloid plaques consisting of amyloid beta (52). Alzheimer's disease is now understood as a continuum of pathological processes that begin decades before the first clinical signs appear. The accumulation of pathological proteins triggers a series of processes that over the years lead to cognitive decline and dementia. Decreased brain metabolism topographically correlates with the accumulation of tau protein or neurodegeneration even before structural imaging reveals signs of atrophy. Cognitive decline occurs with delay; from subjective cognitive complaint through MCI to fully developed dementia (Figure 4) (12,53). Proteinopathy can therefore be demonstrated before the onset of clinical signs.

In addition to imaging, pathological proteins can also be determined in cerebrospinal fluid; AD is characterized by decreased values of amyloid beta and increased values of tau protein and phosphorylated tau protein (p-tau) (55). The sensitivity of the examination for diagnosing AD is 91–93% and the specificity is 81–84% (56). In Slovenia, the examination is available in tertiary neurological centers.

The advantage of imaging using radiopharmaceuticals that bind to amyloid beta

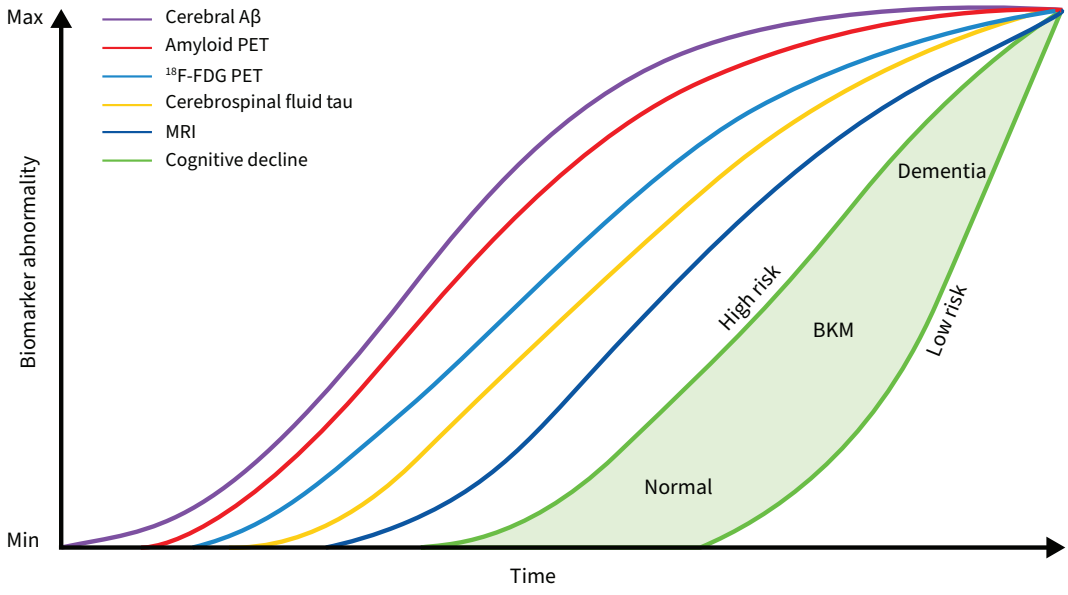

Figure 4: Sequence of pathophysiological processes in Alzheimer's disease (12). Aβ - amyloid beta, MCI - mild cognitive impairment. Adapted from Jack, 2010 (53) and Petersen, 2010 (54).

and protein lies in the non-invasiveness of the examination. And we can also monitor the spatial and temporal distribution of amyloid beta (6). On the other hand, compared to cerebrospinal fluid diagnostics the examination is more expensive. The main importance of proving a pathological substrate *in vivo* is in early and correct diagnosis. Early diagnosis using biomarkers is also a prerequisite for selecting subjects in AD clinical studies to monitor the efficacy of specific treatments (57). Such investigations will have great clinical significance in the future, when causal treatment is available and it may be possible to treat people with AD in the preclinical phase of the disease (6).

Due to the ethical dilemmas posed by investigations because they can confirm the diagnosis of a severe and incurable disease, detailed guidelines with indications for amyloid imaging examinations have been prepared (58,59). Imaging is in place in patients with advanced MCI, in patients with an atypical course, and in patients with dementia, who are under 65 years of age. However, the study does not make sense in elderly patients with a classic clinical picture of dementia in AD, to determine the degree of dementia, nor in healthy subjects with a positive family history and in persons with subjective cognitive complaint (59).

The first and most researched specific amyloid radiopharmaceutical ^{11}C-PiB (19) accumulates in AD primarily in the frontal cortex, cingulate gyrus, precuneus, striatum, parietal and lateral temporal cortex. The occipital, somatosensory, and mesiotemporal cortex accumulates less radiopharmaceuticals, as does the cerebellar cortex (60). This pattern is consistent with the results of histopathological studies of amyloid beta distribution. The evaluation of amyloid imaging is dichotomous regardless of the described pattern of distribution of amyloid beta accumulation: the result is either positive or negative (Figure 5). There are three radiopharmaceuticals labeled with ^{18}F registered for clinical use: ^{18}F-flutemetamol (Vizamyl), ^{18}F-florbetaben (NeuraCeq) and ^{18}F-florbetapir (AMYViD). In patients with AD, they have a similar distribution as ^{11}C-PiB and also distinguish well between AD and healthy subjects (60). Radiopharmaceuti-

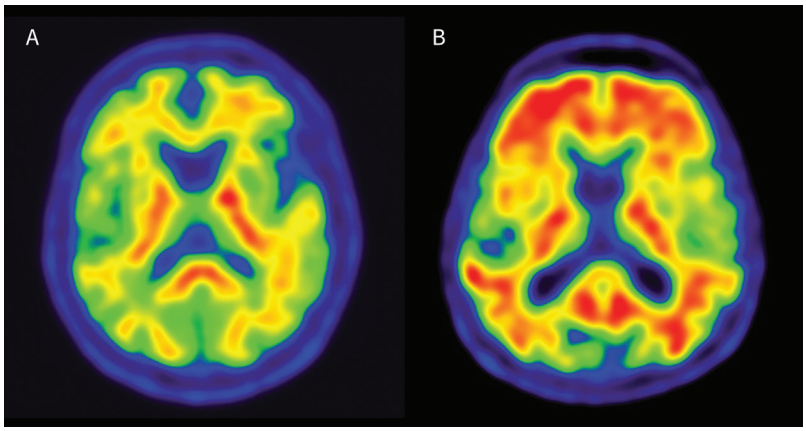

Figure 5: Amyloid PET with ^{18}F-flutemetamol (Vizamyl) in a healthy subject (A) and in a patient with AD (B). In a healthy subject, the radiopharmaceutical binds nonspecifically in the deep white brain and in some deep nuclei, and there is no accumulation in the cerebral cortex. In a patient with AD, the border between the gray and white brain is blurred, the accumulation of radiopharmaceutical is present all the way to the edge of the cerebral cortex (source: Department of Nuclear Medicine, UMC Ljubljana).

cal florbetapir is clinically most commonly used, with a sensitivity of 92% and a specificity of 90.5-100% (61).

For AD subtypes also, such as, e.g. posterior cortical atrophy (PCA) or logopenic variant of primary progressive aphasia (lvPPA), amyloid imaging shows accumulation of amyloid beta. The distribution of amyloid in the brain is similar in all subtypes of AD.

Amyloid beta is also a basic pathophysiological factor in cerebral amyloid angiopathy (CAA), in which it accumulates in the media and adventitia of the leptomeningeal and cortical arteries and arterioles in the central nervous system. This process results in vasculopathy with ischemic events and cerebral hemorrhage. Amyloid imaging can also demonstrate amyloid beta accumulation in CAA, and the accumulation pattern is slightly different than in AD; more of it accumulates occipitally (62).

Amyloid imaging is also positive in about 50% of patients with DLB (63). The accumulation pattern in DLB is similar to that in AD, but the intensity is lower (60). DLB is otherwise characterized by α-syn accumulation. No amyloid beta accumulation was detected in FTD and CJD by amyloid imaging.

3.2 Imaging of tau protein in dementia

In addition to amyloid imaging, in recent years tau imaging has been available, but for now only for research purposes. There are several radiopharmaceuticals available, the most commonly used being AV1451. The distribution of tau in AD and other tauopathies, in contrast to amyloid beta, correlates well with the clinical picture, so tau imaging is also suitable for monitoring disease progression (60).

4 The role of nuclear medicine investigations in the diagnosis of neurodegenerative parkinsonisms

Parkinsonism is a clinical syndrome of bradykinesia with associated stiffness and/or resting tremor (64). It is a central clinical feature of a group of neurodegenerative diseases, among which Parkinson's disease (PD) is the most common. Less common are the so-called parkinsonims plus, in which we detect, in addition to parkinsonism, additional symptoms and signs. These include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB).

Like PD and DLB, MSA is classified as an alpha-synucleinopathy, but in contrast to PD, its characteristics are: poorer response to levodopa therapy, autonomic and in some forms cerebellar involvement (1,65). PSP and CBD are classified as tauopathies. Unlike PD, PSP is characterized by levodopa-unresponsive parkinsonism with associated early postural disorder or falls, vertical eye movement disorders, and cognitive decline (1,66). CBD is distinguished from PD according to a markedly asymmetric clinical picture,

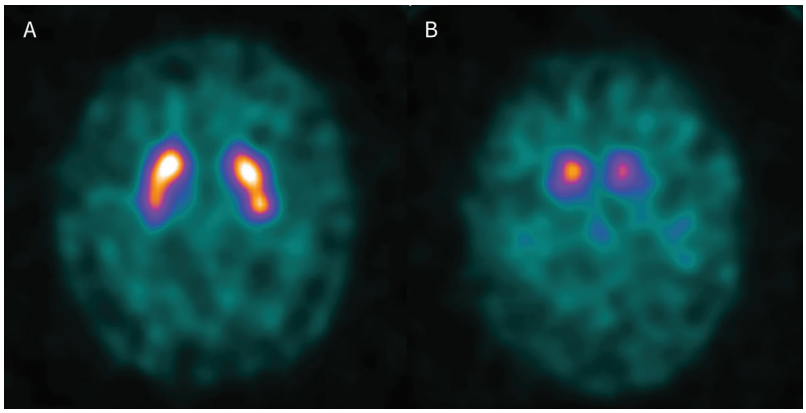

Figure 6: Scintigraphy of a dopamine transporter with 123I-ioflupane (DaTSCAN) in a healthy subject (A) and a patient with Parkinson's disease (B) (source: Department of Nuclear Medicine, UMC Ljubljana).

in which parkinsonism is associated with dystonia, myoclonus, orobuccal apraxia and limb apraxia, cortical sensory failure and alien limb syndrome (1,67).

4.1 Visual representation of the integrity of the dopaminergic system

The diagnosis of PD and other parkinsonisms can be made clinically with considerable accuracy (64). Sometimes, however, it is clinically difficult to distinguish between essential or dystonic tremor and tremor in PD or other parkinsonisms or between neurodegenerative and iatrogenic parkinsonism (68,69). In these cases, scintigraphy of the dopamine transporter with 123I-ioflupane (DaTSCAN, Figure 6) can be crucial. The investigation is also suitable for distinguishing between AD and DLB (36,69), as patients with DLB, similar to other neurodegenerative parkinsonisms, have presynaptic dopaminergic impairment. It sometimes also makes sense to diagnose parkinsonism, which does not progress for a long time, or vascular parkinsonism, in which the result is usually normal, unless the patient has a vascular change in substantia nigra or nigrostriatal connections. When distinguishing between essential tremor and PD, DaTSCAN achieves specificity and sensitivity of about 95% (70), and when distinguishing between DLB and other dementias, 85% or 95% (35).

Some medicines may have some effect on the outcome of DaTSCAN (central nervous system stimulants, some antidepressants, opioids, rotigotine among the dopaminergic drugs), but this effect is relatively small, so they are usually not discontinued before the test (71).

Since the presynaptic dopaminergic system is impaired in all neurodegenerative parkinsonisms, this investigation is not appropriate for distinguishing between them. For this purpose, we need to study the metabolism of the whole brain with ^{18}F-FDG PET with emphasis on the detection of activity in the basal ganglia.

4.2 ^{18}F-FDG PET of the brain in parkinsonism

In contrast to parkinsonism plus, PD is characterized by preserved or even increased metabolic activity in the basal ganglia (primarily the putam and globus pallidus) as a result of a disturbance in the level of inhibitory neurons projecting from the substantia nigra (72) (Figure 7A). Patients with PD have globally reduced cerebral cortex metabolism (73). With disease progression and cognitive decline, cortical hypometabolism deepens as described in the section on PD with dementia.

Statistical network analysis (SSM-PCA method described earlier) have identified a Parkinson's disease related pattern (PDRP) in several independent cohorts of patients with PD in Figure 8, characterized by marked parietooccipital hypometabolism and in the premotor cortex and associated hypermetabolism in the areas of the putamnes, thalamus, brainstem, central cerebellum, and primary sensorimotor cortex (74,75).

In patients with MSA the ^{18}F-FDG PET of the brain shows decreased glucose metabolism in the striatum (especially in the posterior parts of the putamen), in the brainstem, and cerebellum (76). With

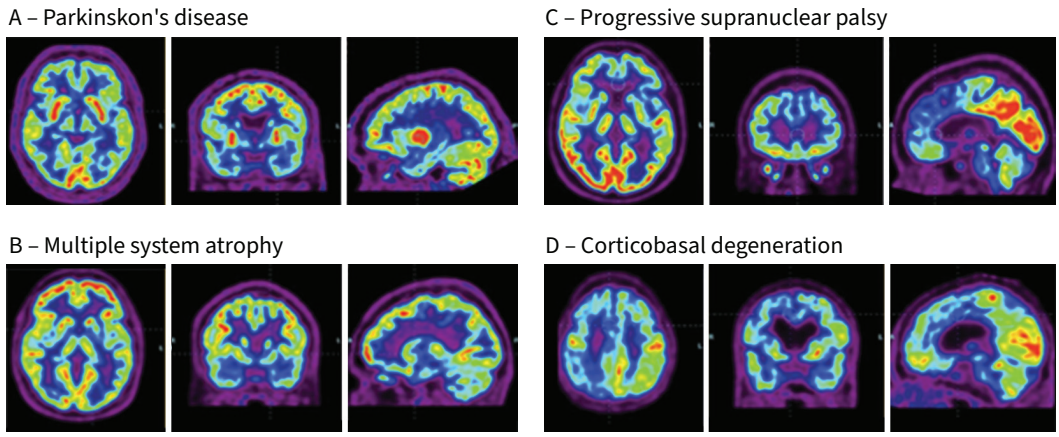

Figure 7: ^{18}F-FDG PET of the brain in (A) Parkinson's disease, (B) multiple system atrophy, (C) progressive supranuclear palsy, and (D) corticobasal degeneration (source: Department of Nuclear Medicine, UMC Ljubljana).

^{18}F-FDG PET of the brain, we can also distinguish between subtypes of MSA: Parkinson's (MSA-P), in which the clinical picture is dominated by parkinsonism (markedly reduced metabolism in the basal ganglia) and cerebellar (MSA-C), in which ataxia is at the forefront (markedly reduced metabolism in the cerebellum) (Figure 7B) (77).

PSP is characterized by marked hypometabolism of the bilateral medial frontal cortex, premotor and prefrontal areas, and striatum (more pronounced in the area of the caput nuclei caudati), in the thalamus, and in the brainstem (Figure 7C) (78).

In CBD the ^{18}F-FDG PET of the brain, according to the clinical picture, shows markedly asymmetric changes in the brain with a more pronounced decrease in metabolic activity on the opposite side from the more affected side. Hypometabolism is usually most pronounced in the parietal cortex, but is also present in the primary somatosensory cortex, medial and lateral premotor area, striatum, and thalamus (Figure 7D) (78).

The metabolic activity of the brain is affected by a number of drugs. Antipsychotics (both classical and newer) are clinically important, as they significantly increase metabolic activity in the basal ganglia (79). Therefore, if neurodegenerative parkinsonism is suspected, it should be noted that the patient is receiving an antipsychotic to avoid the PD-specific false-positive ^{18}F-FDG PET of the brain. Other drugs have no major effect and are not discontinued prior to investigation.

Parkinsonism can be distinguished based on the assessment of ^{18}F-FDG PET of the brain, and the accuracy is significantly increased by using a statistical algorithm that calculates the expression of all Parkinson's patterns in each individual subject. Based on the expression of the patterns, the algorithm calculates the probability of the disease for a particular parkinsonism (28).

5 The role of MRI in diagnosis and parallels to metabolic imaging

In this article, we present the possibilities for the use of functional nuclear medicine imaging to improve the reliability of the established clinical diagnosis. These studies are not performed routinely in all patients, as they are not available in all centers, even in tertiary institutions, they are usually used when faced with a clinical dilemma or with a specific clinical issue. In contrast, structural imaging, such as computed tomography (CT) or magnetic

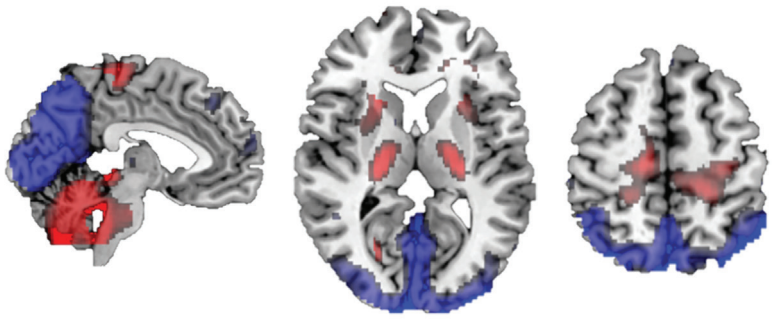

Figure 8: Metabolic pattern of Parkinson's disease (PDRP), identified in a sample of Slovenian patients (75).

resonance imaging (MRI), is the recommended screening method to rule out a possible curable cause of cognitive decline (80). Assessment of brain structure may contribute to improved accuracy of clinical diagnosis. If there are no contraindications, MRI is the method of choice due to its higher resolution and the ability to display a variety of tissue properties. Accurate assessment and the opinion of a neuroradiologist are indispensable in the treatment, and a systematic approach to examining MRI images also helps doctors of other specialties to make a diagnosis.

In the proposed simplified brain MRI screening algorithm, we can first focus on the presence of changes that are not expected in the brain (80). In this way we exclude the presence of a so-called surgical cause of cognitive decline that can be cured. This group mainly includes intracranial tumors and subdural hematoma. An increased amount of otherwise intracranially normally present structure, i.e. cerebrospinal fluid, manifested by enlargement of cerebral ventricles, may also indicate the cause of cognitive impairment. In the differential diagnosis of cognitive disorders or parkinsonisms, such a result of structural imaging and the corresponding clinical picture usually makes us think of normotensive hydrocephalus.

In the next step, we focus on changing the signal, which is generally uniform within the white and gray matter. Elevated white matter signal intensity on T2-weighted and FLAIR (fluid attenuation inversion recovery) sequences may indicate a vascular etiology of cognitive impairment or parkinsonism, and the presence of other signs of small vessel disease, such as lacunar or silent infarcts, may further contribute to the diagnosis (81). Susceptibility weighted imaging (SWI) is a newer MR pulse sequence that provides better contrast due to the different magnetic susceptibility of substances such as iron, blood, and the breakdown products of hemoglobin and calcium (82). Signal changes in SWI may indicate the presence of microbleeds in the context of small vessel disease or amyloid angiopathy. The presence of iron or calcifications may also be a nonspecific indicator of neurodegenerative pathology in dementia and various movement disorders (83). Sensitive for the diagnosis of CJD is the diffusion weighted imaging (DWI), in which an increased signal is found in the area of the cerebral cortex (so-called cortical band) and basal ganglia due to the limited movement of water molecules (50).

In the third step, we evaluate the atrophy pattern by examining the T1-weighted 3D gradient echo sequences in different planes. In AD the atrophy of the medial temporal lobes is most common, but in advanced AD other areas, including the parietal and frontal lobes, are also atrophic (84). In forms of FTD in which speech disorder stands out, the pattern of atrophy is asymmetric - atrophy is more pronounced in the left hemisphere: temporally in svPPA and lvPPA or frontally in nfvPPA (85). In bFTD, atrophy is expressed primarily frontally. It is characteristic of all dementias, however, that with the progression of the disease, along with the appearance of symptoms of impairment of new cognitive domains, there is also a spread of atrophy, which makes structural imaging less indicative in the advanced stage of the disease. Symmetrical generalized atrophy can be accompanied by, for example, AD, DLB and vascular dementia, and to a lesser ex-

tent it can also be expressed in healthy aging (80).

While atrophy on MRI is not particularly pronounced in patients with idiopathic PD without associated dementia, specific patterns of atrophy may contribute to distinguishing idiopathic PD from other parkinsonisms or between individual parkinsonisms plus. PSP is characterized by atrophy of the mesencephalon and frontal lobe. In CBD, MR examination usually reveals asymmetric atrophy frontoparietally, but atrophy of the frontal lobe can also be relatively symmetrical. MSA is characterized by pontocerebellar atrophy (86).

There are many parallels between the patterns of atrophy on structural MR examination and hypometabolism on ^{18}F-FDG PET images of the brain - atrophic areas are usually characterized by lower metabolic activity and vice versa. Nevertheless, the combination of both methods can significantly contribute to the detection of pathological changes and diagnosis (87). Metabolic PET imaging is complemented by some newer MRI methods, which are not yet used regularly in clinical practice. With functional MRI at rest, we can identify the so-called brain's default network. It consists of the brain areas that are most active in the so-called "dormant state" (88). Some neurodegenerative diseases, including AD, are characterized by degradation of this pattern (89). By measuring cerebral blood flow, which is directly dependent on the metabolic activity of the brain, MRI can also provide information similar to ^{18}F-FDG PET of the brain. Various MRI perfusion methods are most often used, such as the T2* and T1 perfusion methods, in which the patient is given the gadolinium contrast agent (Gd-CA). Similar results can be obtained with the arterial spin labeling method, which does not require Gd-CA.

6 Conclusion

Imaging biomarkers of neurodegenerative brain diseases are becoming an increasingly important clinical tool in early diagnosis as well as in research. Nuclear medical imaging can significantly improve the accuracy of the diagnosis of neurodegenerative brain diseases by proving brain pathology in a non-invasive way. With the development of radiopharmaceuticals, the possibilities of demonstrating pathological processes in the brain are constantly expanding.

Due to the diverse and overlapping clinical picture of neurodegenerative proteinopathies, the diagnosis of these diseases is increasingly made with biomarkers. For research purposes, the diagnosis of AD is no longer made on the basis of clinical criteria, but using the so-called A/T/N classification based on the results of amyloid-beta (A) and tau protein (T) accumulation in the brain and evidence of nerve cell damage or neurodegeneration (N) (90). Given the growing role of biomarkers, we expect that in the future diagnoses of neurodegenerative diseases will be based primarily on these findings.

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